Please Note: Part Two of this Review can be found at:
http://www.fda.gov/cber/review/droteli112101r1p2.pdf

Additional product information in reference to this approval can be found at:
http://www.fda.gov/cber/products/droteli112101.htm

FDA CLINICAL REVIEW

DROTRECOGIN ALFA (ACTIVATED)

[RECOMBINANT HUMAN ACTIVATED PROTEIN C (rhAPC)]

XIGRIS™

BLA# 125029/0

Approved: November 21, 2001

U.S. Food and Drug Administration
Clinical Reviewer: LINDA M. FORSYTH, M.D.
Clinical Reviewer: ROBERT LINDBLAD, M.D.
Statistician: JAWAHAR TIWARI, Ph.D.

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Section I-Introduction

Purpose

This clinical review presents data from the clinical studies of drotrecogin alfa (activated) as submitted in Biologics License Application (BLA) application, BLA# 125029/0, from Eli Lilly and Company and an analysis of these data on the safety and efficacy of this product.

Sponsor

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

Product

Recombinant Human Activated Protein C (rhAPC), Drotrecogin alfa (activated), or "Xigris"

Indication

Treatment of severe sepsis.

Background

Sepsis syndrome results from a generalized inflammatory and procoagulant host response to an infection. Proinflammatory cytokines (e.g. tumor necrosis factor, interleukin-1) are capable of activating coagulation and inhibiting fibrinolysis, while the procoagulant thrombin is capable of stimulating multiple inflammatory pathways. Protein C is a circulating plasma zymogen that, in the presence of thrombin, in complex with thrombomodulin (TM) is converted to activated Protein C (APC). APC with Protein S as a cofactor inactivates Factor Va and VIIIa and limits thrombin generation, so APC exerts an antithrombotic effect by inhibiting those factors. *In vitro* data suggest that APC has indirect profibrinolytic activity by its ability to inhibit plasminogen activator inhibitor-1 (PAI-1) and limiting generation of activated thrombin activatable-fibrinolysis-inhibitor. Additionally, *in vitro* data suggest APC exerts an anti-inflammatory effect by inhibiting human tumor necrosis factor production by monocytes, by blocking leukocyte adhesion to selectins, and by limiting the inflammatory responses within the microvascular endothelium induced by thrombin generation. Drotrecogin alfa (activated) and endogenous human APC are inactivated in plasma by endogenous protease inhibitors.

Manufacturing

Drotrecogin alfa (activated) is human APC produced by recombinant DNA technology. The manufacturing process involves the secretion of the inactive Protein C zymogen into the culture medium by an established human cell line into which the complementary DNA for natural human Protein C has been inserted. Human Protein C is enzymatically activated to human APC, subsequently purified and is supplied as a sterile, lyophilized, white to practically white powder. Each vial contains 5 mg or 20 mg of drotrecogin alfa (activated). The lyophilized drug product is initially solvated in water for injection to a concentration of 2 mg/ml followed by dilution into sterile saline (0.9% sodium chloride) for intravenous infusion.

Pharmacokinetics

A variety of infusion rates and duration of infusions were investigated in phase 1 studies using healthy volunteers, subjects with end stage renal disease and other various conditions. Plasma clearance was 28 ± 9 L/hr (mean ± SD, N=190). Elimination was biphasic with a rapid initial phase (t½a=13 minutes) and a slower second phase (t½ß=1.6 hours). The short half-life of 13 minutes accounts for approximately 80% of the area under the plasma concentration curve after stopping infusion and governs the initial rapid rise of plasma rhAPC concentrations towards the steady-state. Plasma rhAPC steady-state concentrations are proportional to the infusion rate over a range of infusion rates from 12 ug/kg/hr to 48 ug/kg/hr. In healthy subjects, greater than 90% of the steady-state plasma concentration is attained within 2 hours following the start of a constant-rate intravenous infusion. In the phase 2 trial, infusions from 12 ug/kg/hr to 30 ug/kg/hr rapidly produced steady-state plasma concentrations that were proportional to infusion rates. Results of phase 2 and phase 3 studies indicate that Cl_p in patients with severe sepsis is higher than that in normal healthy subjects. In the phase 3 trial, pharmacokinetics were evaluated in 342 patients administered a 96-hour continuous infusion at 24 ug/kg/hr. Elimination half-lives were not calculated in patients with sepsis; instead the pharmacokinetic profile of rhAPC was characterized by clearance and C_{ss}. Pharmacokinetics were characterized by attainment of steady-state plasma concentration within 2 hours following the start of the infusion and in the majority of patients, measurements of rhAPC beyond 2 hours after termination of the infusion were below the quantifiable limit (<10 ng/mL), suggesting rapid elimination of drotrecogin alfa from the systemic circulation. Clearance was reported to be 42 L/hour in the phase 3 study (EVAD) with an infusion of 24 ug/kg/hr and 46 ± 38 L/hour for phase 2 studies up to 30 ug/kg/hr for 24 hours (mean ± SD).

Brief Description of Studies

Phase 1 Studies

Described below are the phase 1 studies that were conducted assessing the pharmacokinetic and pharmacodynamic parameters and one safety trial in patients with purpura fulminans.

- ---------- **Clinical Pharmacology**

This was an open-label, single center study in healthy male adults. Three single 3 hour intravenous (iv) infusions per patient at 0.49-25.7 ug/kg/hr rhAPC in 4 males were studied.

- ---------- **Clinical Pharmacology**

This was an open-label, single center study in healthy male adults. Three single 3-hour iv infusions per patient, separated by 2 weeks, at 6.04-49.1 ug/kg/hr rhAPC in 4 patients were studied.

- ---------- **Clinical Pharmacology**

This was an open-label, single center study in healthy adult males and postmenopausal or surgically sterile females, with or without supplemental estrogen. Two dosing periods, 6 and 24-hour iv infusions, separated by at least 14 days, at 6.59-24.2 ug/kg/hr rhAPC in 32 patients were studied.

- ---------- **Clinical Pharmacology**

This was an open-label, single center study in healthy adult males and postmenopausal females, with and without supplemental estrogen. Two dosing periods, 6 and 24-hour iv infusions, separated by at least 5 days, at 12.8-49.9 ug/kg/hr rhAPC in 51 patients were studied.

- ---------- **Clinical Pharmacology**

This was an open-label, single center study in adults with end-stage renal disease (hemodialysis and peritoneal dialysis). One 6-hour infusion at 26.3 ug/kg/hr rhAPC in 12 patients was studied.

- ---------- **Clinical Pharmacology**

This was an open-label, single center study in healthy adults. There were two parts, Part A, single dose aspirin (500 mg po) alone was studied in 15 patients. Part B, single-blind, crossover design, two treatments, separated by at least 14 days, comparing rhAPC in the presence of -------- or placebo was studied in 27 patients. ------ or placebo (po) was followed by 6-hour infusion at 25.1 ug/kg/hr rhAPC.

- ---------- **Clinical Pharmacology**

This was an open-label, single center study in healthy adult males. Part A-bolus dose of up to 10 µg/kg over 1 minute with/without subsequent infusion at a rate of 12 µg/kg/hr for 6 hours was studied in 6 patients. Part B-a two-step infusion of 18 µg/kg/hr for 30 minutes followed by 12 µg/kg/hr for 6.5 hours, and a three-step infusion of 24 µg/kg/hr

for 15 minutes then 16 µg/kg/hr for 45 minutes followed by 12 µg/kg/hr for 6.0 hours was studied in 6 patients (1 re-entered from part A). Average infusion rates were 12.3 (over 2 infusions) or 12.8 ug/kg/hr (over 3 infusions).

- ---------- **Clinical Pharmacology**

This was an open-label, single center study in healthy adult males and postmenopausal females in 14 patients. One single 0.5 hour loading dose followed by a 5.5-hour constant rate iv infusion of rhAPC was given. Average infusion rates over two infusions were 12.5, 24.7 or 49.8 ug/kg/hr.

- ---------- **Clinical Pharmacology**

This was an open-label, single center study in healthy adult controls and patients with end-stage renal disease requiring hemodialysis or peritoneal dialysis for more than 3 months. 13 patients were studied at 6-hour infusions for control and treatment groups, with hemodialysis group receiving two infusions (1 and 2 days after hemodialysis) at 24 ug/kg/hr rhAPC.

- ---------- **Clinical Pharmacology**

This was an open-label, multicenter study in adults with end-stage renal disease requiring hemodialysis for more than 3 months. 5 patients, with 3 sessions of hemodialysis with control and 3 sessions with rhAPC were evaluated. rhAPC: a loading dose followed by continuous infusion of 24 ug/kg/hr for 6 hours was studied. Control: standard heparin protocol for hemodialysis.

- ---------- **Clinical Pharmacology**

This was a single-blind, placebo-controlled study in healthy adults. 13 patients with two of three possible infusion rates during 3 separate study periods were evaluated. rhAPC was given with infusion rates of 12, 24 or 48 ug/kg/hr and placebo was saline.

- ---------- **Purpura fulminans noncontrolled study**

This was an open-label, multicenter study in adults and pediatric patients with purpura fulminans. 35 subjects enrolled, from 8 month-61 years, at 19 centers. 96 to 168-hour continuous iv infusion of 24 ug/kg/hr rhAPC was studied. Safety profile included 28-day follow up.

- ---------- **Protein C deficiency noncontrolled study**

This was an open-label, single center study in adults with heterozygous Protein C deficiency (HPCD). Up to three 24-hour iv infusions each, separated by a minimum of 3 weeks in 9 patients were studied. rhAPC was given at a range of doses between 0.48 and 24 ug/kg.

Phase 2 Studies

- **---------- Pediatric patients noncontrolled study**

This was an open-label, multicenter trial in pediatric patients with severe sepsis. In the interim report sixty patients, age 1 day-17 years, at 9 centers had been studied. The study was conducted in two parts. In part 1, rhAPC was administered at 6, 12, 24 or 36 ug/kg/hr for 6 hours once daily for a 4-day treatment in 23 patients. In part 2, 96-hour infusion at 24 ug/kg/hr (based on Part 1 results) was studied in 37 patients.

- **---------- Placebo-controlled study**

This was a randomized, double-blind, placebo-control, dose-ranging study in adults with severe sepsis. 135 patients were enrolled from 40 centers and 131 received study drug. Study was conducted in 2 parts. In Stage 1, 48-hour continuous iv infusion in 72 patients was studied. In Stage 2, 96-hour continuous iv infusion of rhAPC in 59 patients was studied. rhAPC dose-ranging was 12, 18, 24 or 30 ug/kg/hr at 48-hour iv infusion or 12, 18 or 24 ug/kg/hr at 96 hour iv infusion. Placebo used was sterile 0.9% sodium chloride or 5% dextrose water.

Phase 3 Study

- **---------- Placebo-controlled study**

This was a randomized, double-blind, placebo-controlled, multicenter study in adults with severe sepsis. A total of 1728 subjects were enrolled from 164 centers and 1690 patients received study drug. rhAPC was administered at a continuous iv infusion 96 ± 1 hours at 24 ug/kg/hr rhAPC. Placebo used was sterile 0.9% sodium chloride or ---- human serum albumin added to placebo. Primary endpoint of the study was 28-day all-cause mortality status.

Section II – Phase II ---------- Clinical Study

Study Description

The ---------- phase 2 study investigated the safety and pharmacokinetics of rhAPC. The objective of the study was to identify the effective dose range and dose duration of rhAPC in the correction of sepsis-induced intravascular coagulation and in the prevention or improvement of sepsis-induced organ failure. rhAPC or placebo was administered as a continuous intravenous (iv) infusion for 48 or 96 hours to 131 patients with severe sepsis.

Study Design

Primary objectives of the study were to assess the safety of administration of rhAPC as a function of dose and dose duration, to determine the degree to which the coagulation abnormalities of severe sepsis are affected by the administration of rhAPC as a function of dose and dose duration and to determine an effective dose and dose duration of rhAPC administration based on the ability of rhAPC to alter the coagulation abnormalities of severe sepsis, for use in future studies. Secondary objectives were to determine the baseline characteristics (coagulation profile, Protein C antigen level, Protein C functional activity and Factor V Leiden) of patients with severe sepsis which may be predictive of individuals who may benefit from the use of rhAPC; to characterize the pharmacokinetics of rhAPC in patients with severe sepsis; to estimate the effect of rhAPC on organ dysfunction associated with severe sepsis, and transfusion-free, systemic inflammatory response syndrome (SIRS)-free, intensive care unit (ICU)-free days; and 28-day all-cause mortality for patients with severe sepsis. The study was conducted in two sequential steps, designated as Stage 1 and Stage 2, and both were double-blind, placebo-controlled, dose-ranging studies of rhAPC administered as a continuous iv infusion over a fixed interval of 48 hours (Stage 1) and 96 hours (Stage 2). The initial rhAPC dose used in both stages was 12 ug/kg/hr. The starting dose was chosen based on results from three Phase 1 studies. In these studies, the 12 ug/kg/hr dose was shown to be safe and tolerable. In Stage 1 and Stage 2, after the initial dose of 12 ug/kg/hr, subsequent increased doses were determined by the Data Monitoring Board convened to review the available safety, pharmacokinetic, and pharmacodynamic data. A total of 72 patients received study drug in Stage 1 and total of 59 patients in Stage 2. The study included 131 patients total, of whom 41 received placebo and 90 received rhAPC, infused at rates ranging from 12 to 30 ug/kg/hr for 48 or 96 hours.

Efficacy

Percent mortality by treatment group is shown below in Table 1. A 15% relative risk reduction in 28-day all-cause mortality was observed when comparing rhAPC-treated patients with all placebo-treated patients (29% versus 34%, chi-square test, p=0.55).

The sponsor noted that a 40% relative risk reduction was observed when comparing the high dose rhAPC-treated patients (24 and 30 ug/kg/hr) with placebo-treated patients (21% versus 34%). However, these were retrospective analyses, and no consistent dose effects were seen in this relatively small study.

An analysis of adverse events and bleeding rates suggest the dose of 24 ug/kg/hr rhAPC yielded an improved safety profile as compared to 30 ug/kg/hr or lower doses of 12 and 18 ug/kg/hr. During the period of drug infusion for Stages 1 and 2, the percentage of patients experiencing at least one treatment-emergent adverse event was 46% in the groups given doses of 24 ug/kg/hr and 30 ug/kg/hr rhAPC versus 75% for patients given 12 and 18 ug/kg/hr; in patients given placebo, treatment-emergent adverse events occurred in 61% of the cases. Additionally, 30% (N=8) of the patients dosed at 24 ug/kg/hr rhAPC versus 50% (N=6) of those dosed at 30 ug/kg/hr experienced an elevated whole blood APTT and required reductions in dosing during the first 48 hours of infusion. When indicators of pharmacological activity such as d-dimer concentrations or interleukin (Il)-6 levels during the period of infusion were considered, they supported the dose of 24 ug/kg/hr and an infusion period of 96 hours.

Table 1. Percent mortality by treatment group

Treatment	**N**	**Mortality N (%)**
High rhAPC doses		
rhAPC 30 ug/kg/hr 48 hour duration	12	3 (25)
rhAPC 24 ug/kg/hr 96 hour duration	15	5 (33)
rhAPC 24 ug/kg/hr 48 hour duration	12	0 (0)
Total	39	8 (21)
Low rhAPC doses		
rhAPC 18 ug/kg/hr 96 hour duration	15	7 (47)
rhAPC 18 ug/kg/hr 48 hour duration	11	3 (27)
rhAPC 12 ug/kg/hr 96 hour duration	14	5 (36)
rhAPC 12 ug/kg/hr 48 hour duration	11	3 (27)
Total	51	18 (35)
Total of all rhAPC patients	**90**	**26 (29)**
Placebo 48 hour duration	26	10 (38)
Placebo 96 hour duration	15	4 (27)
Total of all placebo patients	**41**	**14 (34)**
Total number of phase 2 patients	131	40 (31)

rhAPC vs. placebo p=0.545

Presented below are safety data on dosing from the phase 2 trial.

Table 2. Safety Phase 2: patient deaths by treatment group

Treatment group	48 hour infusion	96 hour infusion
12 ug/kg/hr	3/11 (27%)	5/14 (36%)
18 ug/kg/hr	3/11 (27%)	7/15 (47%)
24 ug/kg/hr	0/12 (0%)	5/15 (33%)
30 ug/kg/hr	3/12 (25%)	Not studied
All placebo	14/41 (34%)	

Table 3. Serious adverse events (SAE) during infusion period by treatment group

Treatment group	N (%)
48 hour rhAPC	7/46 (15%)
96 hour rhAPC	12/44 (27%)
All placebo	10/41 (24%)

Two classifications of bleeding events were employed in this study. Significant bleeding events were recorded separately from bleeding events meeting the definition of a serious adverse event in order to assess any potential relationship between bleeding complications and the administration of rhAPC.

The number of bleeding events reported as significant were 3/90 (3%). There were no intracranial hemorrhages reported. Three of the 90 patients who got active drug experienced a bleed that was reported as significant. A significant bleeding event was defined as any of the following occurring during the infusion of study drug or within a 2-day period after discontinuation of the study drug infusion:

1. Persistent and difficult-to-control oozing or bleeding from previous needle puncture sites or indwelling catheters or any other visible source.
2. The need for transfusion of two or more units of packed red blood cells (PRBCs) on any 2 consecutive days.
3. Persistent hemoptysis or the expectoration of more than 150 mL of blood in a 12-hour period.
4. Persistent hematemesis (red blood or guaiac-positive "coffee grounds") that did not clear with a 1.5 L gastric lavage.
5. Any intracranial hemorrhage.

A serious adverse event was defined as any event that resulted in death, overdose, was life-threatening, caused severe or permanent disability, required or prolonged hospitalization, resulted in any congenital abnormality, caused cancer, or suggested (other than those meeting the definition of serious) a significant hazard, contraindication, side effect, or precaution as determined by the investigator or study clinical research physician, irrespective of drug causality. For the purpose of assessing the incidence of serious adverse events (SAEs) occurring during the study drug infusion period, the study drug infusion period was defined as Study Day 0 through Study Day 4 for Stage 1 patients and Study Day 0 through Study Day 6 for Stage 2 patients. These time intervals

included the anticipated study drug infusion period plus 2 days. A total of 29 patients (22%) experienced at least 1 SAE with onset occurring during the study drug infusion period.

Section III – Phase III ---------- Clinical Study

Study Description

The ---------- phase 3 study was a randomized, double-blind, placebo-controlled, multicenter, study of rhAPC administered as a continuous 96-hour intravenous infusion in patients with severe sepsis. The efficacy, safety, and pharmacokinetics of a 96-hour infusion of rhAPC were evaluated using a dose of 24 ug/kg/hr. Patients were randomly assigned in a 1:1 ratio to receive either rhAPC or placebo. Approximately 2280 patients were planned to be enrolled in the study. The primary objective of the study was to demonstrate rhAPC reduces 28-day all-cause mortality in patients with severe sepsis. Secondary objectives were to show that rhAPC reduces 28-day all-cause mortality in patients with severe sepsis and Protein C deficiency at baseline, to evaluate the effects of rhAPC on organ function (cardiovascular, respiratory, renal, hematologic, and hepatic), to evaluate the health economic impact of rhAPC administration in patients with severe sepsis and to further characterize the pharmacokinetics. Clinical laboratory tests performed included hematology and clinical chemistry, platelets, activated partial thromboplastin time (APTT), prothrombin time (PT), D-dimer, Il-6 level, APC resistance, APC level, Protein C (PC) functional activity, anti-APC antibody, antithrombin functional activity and Protein S functional activity.

Study Design

There were two separate window periods prior to study drug administration to be met for study eligibility. Window I was a 24-hour time frame before enrollment during which patients were screened to determine eligibility for study entry. Patients who met all of the inclusion criteria and did not meet any of the exclusion criteria were eligible for entry in the study. Window II was a 24-hour time frame during which the baseline efficacy and safety assessments were performed before start of the study drug. Patients randomly assigned to the placebo were to receive -------- human serum albumin (HSA) solution for 96 hours (although for part of the study patients randomized to placebo received 0.9% saline). The primary efficacy endpoint in this study is mortality status through the 28 days (672 hours) after the initiation of study drug infusion. All patients who received study drug for any length of time were followed to determine 28-day survival status, regardless of whether they were withdrawn from study drug.

Selection of Study Population

Described in detail below are patients with severe sepsis with the inclusion and exclusion criteria used to select the study population.

Phase 3 Inclusion Criteria

For the purposes of this study, patients with severe sepsis were defined as having:

1. Three or more SIRS criteria (Criteria A)
2. At least one of the five organ failure criteria (Criteria B)
3. Evidence of infection (Criteria C)

Criteria A (modified SIRS entry criteria):

The patient must have had three or more of the following qualifications during Window I. The events satisfying these criteria must have been attributable to the onset of sepsis and not attributable to an underlying disease process or to the effects of concomitant therapy.

1. Core temperature =38°C (100.4°F) or =36°C (96.8°F). Core temperature was defined as rectal, central catheter, or tympanic. If oral or axillary temperature was used, 0.5°C (1°F) was added to the measured value. Hypothermia (=36°C or 96.8°F) must have been confirmed by a rectal or core temperature.
2. Heart rate =90 beats/min. If patients had a known medical condition or were receiving treatment that would prevent tachycardia (for example, heart block or beta blockers), they need only have met two of the three remaining Criteria A, excluding heart rate.
3. Respiratory rate =20 breaths/min or a PaCO2 =32 mm Hg, or mechanical ventilation or an acute process.
4. White blood cell count of =12,000/mm^3 or =4,000/mm^3 or >10% immature neutrophils.

Criteria B (associated organ failure entry criteria):

The patient must have met one or more of the following criteria during Window I. This criterion must have been newly developed in the context of the changes listed in Criteria A, and not explained by underlying disease processes or by effects of concomitant therapy.

1. **Cardiovascular**: An arterial systolic blood pressure (SBP) of =90 mm Hg or a mean arterial pressure (MAP) =70 mm Hg for at least 1 hour despite adequate fluid resuscitation, adequate intravascular volume status, or the need for vasopressors to maintain SBP =90 mm Hg or MAP =70 mm Hg. Adequate fluid resuscitation or adequate intravascular volume was defined as one or more of the following:
   a) Pulmonary arterial wedge pressure =12 mm Hg
   b) Central venous pressure =8 mmHg.
      Note: Vasopressors were defined as:
      - Dopamine =5 ug/kg/min
      - Norepinephrine, epinephrine, or phenylephrine at any dose.
      - Note: Dobutamine and Dopexamine were not considered vasopressors.
2. The administration of an intravenous fluid bolus (500 mL of crystalloid solution, =20 g of albumin, or =200 mL of other colloids administered over 30 minutes or less).
3. **Renal**: Urine output <0.5 mL/kg/hr for 1 hour, despite adequate fluid resuscitation as described. In the presence of preexisting impairment of renal function (defined as a serum creatinine concentration > 2 times the upper limit of the normal reference range for that institution prior to the onset of sepsis), the patient must have met one of the other four organ failure criteria.
4. **Respiratory**:
   a) PaO2 /FiO2 =250
   b) If the lung was the sole organ meeting criteria as well as the suspected site of infection, the patient must have had a PaO2 /FiO2 =200.
5. **Hematology**: Platelet count of <80,000/mm^3 or a 50% decrease in the platelet count from the highest value recorded over the previous 3 days.
6. **Unexplained metabolic acidosis**, which was defined as:
   a) pH =7.30 or base deficit =5.0 mEq/L and
   b) A plasma lactate level >1.5 times the upper limit of normal for the reporting lab.

Criteria C (infection criteria): The development of SIRS and associated organ failure must have been secondary to an infection.

Suspected or proven infection. Patients with suspected infection must have had evidence of an infection such as white blood cells in a normally sterile body fluid, perforated viscus, chest x-ray consistent with pneumonia and associated with purulent sputum production, or a clinical syndrome associated with a high probability of infection (for example, ascending cholangitis).

Phase 3 Exclusion Criteria

Patients were excluded from the study for any of the following reasons:

1. Pregnant or breastfeeding.
2. Less than 18 years of age.
3. Weighing >135 kg.
4. Platelet count < 30,000/mm^3.
5. Increased risk for bleeding (for example):
   a) Any patient who had undergone major surgery, defined as surgery that required general or spinal anesthesia that was performed within the 12-hour period immediately preceding study drug infusion; any postoperative patient who demonstrated evidence of active bleeding; or any patient with planned or anticipated surgery during the study drug infusion period, such as patients with staged surgeries or burn patients with planned excisions and grafting during the study drug infusion period.
   b) History of severe head trauma that had required hospitalization, intracranial surgery, or stroke within 3 months of study entry, or any history of intracerebral arteriovenous malformation, cerebral aneurysm, or central nervous system mass lesion. Patients with an epidural catheter or who anticipated receiving an epidural catheter during study drug infusion were also excluded from the study.
   c) History of congenital bleeding diatheses, such as hemophilia.
   d) Gastrointestinal bleeding within 6 weeks of study entry that required medical intervention unless definitive surgery had been performed.
   e) Trauma patients at increased risk of bleeding, for example: flail chest; significant contusion to lung, liver, or spleen; retroperitoneal bleed; pelvic fracture; or compartment syndrome.
6. Patients with a known hypercoagulable condition including activated Protein C resistance; a hereditary deficiency of Protein C, Protein S, or antithrombin; presence of anticardiolipin antibody, antiphospholipid syndrome, lupus anticoagulant or homocysteinemia; or patients with a recently documented (within 3 months of study entry) or highly suspected deep venous thrombosis or pulmonary embolism.
7. Patients taking the following medications:
   a) Therapeutic heparin, defined as:
      - Unfractionated heparin dosed to treat an active thrombotic or embolic event within the 8 hours prior to study drug infusion.
      - Low molecular weight heparins used at any dose higher or more frequent than the recommended dose in the product label for prophylaxis within the 12 hours prior to study drug infusion.
      - Note: Prophylactic unfractionated heparin up to 15,000 units/day was permitted.
   b) Warfarin, if used within 7 days of study entry and if prothrombin time was prolonged beyond the upper limit of normal for the institution.

c) Acetylsalicylic acid (ASA) >650 mg/day or compounds that contain ASA >650 mg/day within 3 days of study entry.
d) Thrombolytic treatment within 3 days of study entry (for example, streptokinase, tPA, rPA, and urokinase).
Note: These agents were permitted for the treatment of intra-catheter thromboses; however, care should have been taken to avoid systemic administration.
e) Glycoprotein IIb/IIIa antagonists within 7 days of study entry.
f) Antithrombin infusion of >10,000 units within 12 hours of study entry.
g) Protein C infusion within 24 hours of study entry.

8. Participation in another therapeutic drug or device trial or use of another investigational agent, such as nitric oxide, within 30 days of study entry without prior approval from the Vanderbilt Coordinating Center (VCC).
9. Patients with known esophageal varices, chronic jaundice, cirrhosis, or chronic ascites.
10. Presence of an advanced directive to withhold life-sustaining treatment with the exception of cardiopulmonary resuscitation (CPR).
11. Patients not expected to survive 28 days given their preexisting, uncorrectable medical condition. This criterion included patients with, or suspected to have, poorly controlled neoplasms or other end-stage processes, such as end-stage cardiac disease, prior cardiac arrest, end-stage lung disease, or end-stage liver disease. Enrollment of patients with known or suspected metastatic cancer was approved by the VCC prior to randomization. Lilly provided guidelines for the VCC to use in determining which patients with malignancy were appropriate for this study.
12. Patients with chronic renal failure on either hemodialysis or peritoneal dialysis.
Note: Patients with acute renal failure were permitted.
13. HIV positive patients who's most recent CD4 count, if known, was =50/mm^3.
14. Patients who had undergone bone marrow, lung, liver, pancreas, or small bowel transplantation.
15. Patients who were moribund and where death was perceived to be imminent (within 24 hours).
16. Presence of the first sepsis-induced organ failure greater than 24 hours prior to the start of Window II.
17. Patients whose family or primary physician had not committed to aggressive management of the patient.
18. Patients with acute clinical pancreatitis without a proven source of infection.

Statistical Plan

The primary efficacy analysis was based on the Cochran-Mantel-Haenszel test stratified by pre-infusion acute physiology and chronic health evaluation (APACHE) II quartile, age class and baseline Protein C activity class for the intent-to-treat (ITT) (with pooling of under-represented strata). The relative risks and corresponding confidence interval, were calculated using the logit adjusted relative risk method with an adjustment for pre-infusion APACHE II quartile, age class, and baseline Protein C activity class (with pooling of under-represented strata). A Data and Safety Monitoring Board (DSMB), external to the sponsor, was established to evaluate interim data and had the authority to recommend trial suspension if safety concerns arose or if the predictive probability of establishing efficacy was low and to recommend trial termination for efficacy according to pre-specified criteria. The following subgroup analyses were performed:

- Protein C deficiency status (>80%, =80%)
- baseline Protein C activity class (unknown, >80%, >60 to 80%, >40 to 60%, and =40%)
- antithrombin (AT) III deficiency status
- AT III quartile
- APACHE II quartile
- age class (<60, ≥60 years)
- gender
- country of investigative site
- investigative site
- origin
- instrumental Activities of Daily Living (ADL) index quartile
- renal, respiratory, cardiovascular, coagulation, unexplained metabolic acidosis organ failure criteria status
- number of systemic inflammatory response syndrome (SIRS) criteria met at baseline (3 or 4)
- number of organ failure criteria met (1, 2, 3, 4 or 5)
- cardiovascular, renal, coagulation, respiratory, liver organ dysfunction/failure (SOFA score)
- septic shock status
- acute respiratory distress syndrome (ARDS) status
- disseminated intravascular coagulation (DIC) status
- invasive mechanical ventilation status
- time from meeting Criteria A, B and C to initiation of study drug (<12 hours, 12-24 hours)
- time from first sepsis induced organ failure to start of study drug administration (24 hours, >24 hours)
- immunocompromised (yes/no)
- APC resistance (yes/no)
- actual infection confirmed by a positive culture (yes/no)
- positive blood culture (yes/no)

Results of Interim Analyses

The study design included two planned interim analyses, which occurred shortly after 760 patients and 1520 patients were enrolled, received study drug, and completed the protocol. The statistical guidelines to suspend study enrollment for efficacy with respect to 28-day mortality followed the O'Brien-Fleming[1] method as implemented by Lan and DeMets[2]. The first interim analysis occurred in October 1999 and the second interim analysis in June 2000. The pre-specified two-sided critical alpha levels for the first and second interim analyses were 0.0002 and 0.0118 respectively. After the second interim, which included a review of 1520 patients who had received rhAPC or placebo, the DSMB recommended that study enrollment be suspended because of a statistically significant reduction in 28-day all-cause mortality in rhAPC-treated patients compared with placebo-treated patients. Data from 1520 patients showed 192 of the 768 (25%) rhAPC-treated patients and 236 of the 752 (31%) placebo-treated patients did not survive 28 days (primary stratified analysis p=0.0071, nonstratified p=0.0057). Trial enrollment was suspended on 28 June 2000. At the time of enrollment suspension, 1728 patients already had been enrolled, 1690 patients had received the study drug for any length of time and constituted the intent-to-treat (ITT) population for the study.

Removal of Patients from Therapy or Assessment

Patients were considered to have completed the protocol if their 28-day survival status was available. Thirty-eight patients were discontinued from the study before receiving study drug. Of these, thirty-seven patients were followed for 28-day survival status, although they were not considered to have completed the protocol. One patient was lost to follow up, Patient ----------, who was assigned to rhAPC treatment.

[1] Biometrics 35:549-556, 1979.
[2] Biometrika 70:659-663, 1983.

Section IIIA-Baseline characteristics

The data presented in the following tables summarize the baseline characteristics and demographics found in both the rhAPC and placebo groups.

Gender

Below is a summary of gender in both treatment groups and in the total number of patients.

Table 4. Baseline distribution of gender

Gender	rhAPC (850) N (%)	Placebo (840) N (%)	Total N (1690) N (%)
Female	373 (44)	353 (42)	726 (43)
Male	477 (56)	487 (58)	964 (57)

Age

Below is a summary of the age classes in both treatment groups and in the total number of patients.

Table 5. Baseline distribution of age

Age Classification (years)	rhAPC (850) N (%)	Placebo (840) N (%)	Total N (1690) N (%)
<60	375 (44)	366 (44)	741 (44)
≥60	475 (56)	474 (56)	949 (56)
<65	437 (51)	449 (54)	886 (52)
≥65	413 (49)	391 (47)	804 (48)
<75	645 (76)	659 (79)	1304 (77)
≥75	205 (24)	181 (22)	386 (23)

Ethnic Origin

Below is a summary of the ethnic origin of the patient in both treatment groups and in the total number of patients.

Table 6. Baseline distribution of ethnic origin

Ethnic origin	rhAPC (850) N (%)	Placebo (840) N (%)	Total N (1690) N (%)
African descent	70 (8)	61 (7)	131 (8)
Western Asian	5 (1)	6 (1)	11 (1)
Caucasian	695 (82)	689 (82)	1384 (82)
East/Southeast Asian	9 (1)	13 (2)	22 (1)
Hispanic	34 (4)	40 (5)	74 (4)
Other	37 (4)	31 (4)	68 (4)

The data presented above show well-balanced treatment groups with respect to gender, age and ethnic origin.

Disease Severity

Presented below is a summary of the conditions accompanying severe sepsis and the APACHE II scores at baseline found in the treatment groups.

Table 7. Baseline distribution of disease severity

Variable	rhAPC (850) N (%)	Placebo (840) N (%)	Total N (1690) N (%)
Shock[1]			
No	252 (30)	238 (28)	490 (29)
Yes	598 (70)	602 (72)	1200 (71)
ARDS[2]			
No	725 (85)	706 (84)	1431 (85)
Yes	125 (15)	134 (16)	259 (15)
DIC[3]			
DIC	800 (94)	774 (92)	1574 (93)
No DIC	49 (6)	66 (8)	115 (7)
Unspecified	1	0	1
Ventilation			
No	227 (27)	188 (22)	415 (25)
Yes	623 (73)	652 (78)	1275 (75)
Immunocompromised[4]			
No	763 (90)	771 (92)	1534 (91)
Yes	87 (10)	69 (8)	156 (9)
Pre-infusion APACHE II			
Mean (range 3-53)	25	25	25
Median	24	24	24

[1] Septic shock is defined under the cardiovascular organ failure as described in inclusion/exclusion criteria: arterial systolic blood pressure (SBP) of less than or equal to 90 mm Hg or mean arterial pressure (MAP) of less than or equal to 70 mm Hg) in the phase 3 inclusion criteria.

[2] Patients were defined as having acute respiratory distress syndrome (ARDS) at baseline if each of the following three criteria were present within 24 hours prior to the start of study drug infusion: chest x-ray shows bilateral infiltrates consistent with pulmonary edema on the frontal chest radiograph (these infiltrates may be patchy, diffuse, homogeneous or asymmetric but not explained by tumor, pleural effusion or simple atelectasis); at the time of the chest x-ray, the central venous pressure, pulmonary capillary wedge pressure or clinical assessment did not indicate central venous volume overload; or PaO2/FiO2 less than or equal to 200.

[3] Patients were defined as having disseminated intravascular coagulation (DIC) at baseline if they had, if any 2 of the following 4 criteria were met within 24 hours prior to initiating study drug infusion: platelet count <100,000/mm^3 or a 50% decrease from any value in the last 3 days; prothrombin time or activated partial thromboplastin time >1.2 times the upper limit of normal (ULN); evidence of procoagulant and/or fibrinolytic activation based on a D-dimer >ULN; or evidence of inhibitor consumption based on either protein C activity, protein S activity or antithrombin III activity below the lower limit of normal.

[4] Immunocompromised was defined as patients who received treatment that suppresses resistance to infection, eg. immunosuppression chemotherapy, radiation, long-term recent high-dose steroids (>0.3 µg/kg/day of prednisone or equivalent daily for 6 months), or had a disease that was sufficiently advanced to suppress resistance to infection, such as leukemia, lymphoma, or AIDS.

The mean APACHE II scores between rhAPC and placebo were the same. The percentage of patients requiring ventilation was higher in placebo 78% vs. 73% with rhAPC. The number of patients requiring vasopressors was 72% rhAPC and 76% placebo. The number of patients requiring dobutamine was 14% both on rhAPC and placebo.

Reviewer comment: Of note, 71% of the patients had shock and 93% of the patients had disseminated intravascular coagulation (DIC) as defined by the sponsor at baseline. The definitions are not entirely consistent with the standard definitions of DIC and shock. This has implications regarding the outcomes of these subgroups as will be discussed later.

Pre-infusion SIRS and Organ Failure Status

Presented below is a summary of the number of patients that met systemic inflammatory response syndrome (SIRS) criteria and organ failures (OF) criteria at baseline within the respective treatment groups.

Table 8. Baseline distribution of pre-infusion SIRS and organ failure status [1]

Variable	rhAPC (850)	Placebo (840)	Total N (1690)
Number of SIRS[2] criteria met			
2	3 (0)	3 (0)	6 (0)
3	341 (40)	324 (39)	665 (39)
4	506 (60)	513 (61)	1019 (60)
Number of Organ Failure (OF) met			
0	1 (0)	0	1 (0)
1	215 (25)	203 (24)	418 (25)
2	270 (32)	273 (33)	543 (32)
3	214 (25)	218 (26)	432 (26)
4	119 (14)	116 (14)	235 (14)
5	31 (4)	30 (4)	61 (4)
Cardiovascular OF met			
No	248 (29)	228 (27)	476 (28)
Yes	602 (71)	612 (73)	1214 (72)
Respiratory OF met			
No	218 (26)	200 (24)	418 (25)
Yes	632 (74)	640 (76)	1272 (75)
Hematology OF met			
No	712 (84)	710 (85)	1422 (84)
Yes	138 (16)	130 (16)	268 (16)
Renal OF met			
No	493 (58)	487 (58)	980 (58)
Yes	357 (42)	353 (42)	710 (42)
Acidosis OF Met			
No	551(65)	558 (66)	1109 (66)
Yes	299 (35)	282 (34)	581 (34)
Type of OF at study entry in patients with single OF			
Cardiovascular	66 (8)	58 (7)	124 (7)
Hematology	6 (1)	6 (1)	12 (1)
Acidosis	11 (1)	7 (1)	18 (1)
Renal	19 (2)	14 (2)	33 (2)
Respiratory	113 (13)	118 (14)	231 (14)

[1]The mean time from first organ failure to study drug administration was 18 hours for the rhAPC group and 17 hours for the placebo group.

[2]Systemic inflammatory response syndrome (SIRS)-the body's physiological response to conditions include trauma, burns, pancreatitis, and infection develops as a consequence of infection is referred to as sepsis. SIRS was defined as under the inclusion criteria for phase 3 (at least 3 of 4: temperature; heart rate-tachycardia (e.g. heart block or beta blockers need only meet 2 of the 3 other criteria); respiratory rate or acute mechanical ventilation; or white blood cells).

Treatment groups are well-balanced with respect to organ failure distribution. The data presented above show 25% of the patients had one organ failure at the time of entry criteria prior to the start of infusion. The most common single failure at entry was respiratory failure at 14%.

Baseline SOFA Scores

Sequential Organ Failure Assessment (SOFA)[3] uses a scoring system from 0 (normal)-4 (most abnormal). SOFA scores were based on local laboratory data, vasopressor dosages, and the need for mechanical ventilation. Organ dysfunctions assessed using the SOFA methodology included respiratory, coagulation, liver, cardiovascular, and renal.

SOFA Scoring System

	SOFA Score				
	0	1	2	3	4
Respiration					
Pao_2/Fio_2 (torr)	>400	≤400	≤300	≤200 With respiratory support	≤100 With respiratory support
Coagulation					
Platelets ($\times 10^3/mm^3$)	>150	≤150	≤100	≤50	≤20
Liver					
Bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
(μmol/L)	<20	20–32	33–101	102–204	>204
Cardiovascular					
Hypotension	No hypotension	MAP <70 mm Hg	Dopamine ≤5 or dobutamine (any dose)[a]	Dopamine >5 or epi ≤0.1 or norepi ≤0.1[a]	Dopamine >15 or epi >0.1 or norepi >0.1[a]
Central Nervous System					
Glasgow Coma Score	15	13–14	10–12	6–9	<6
Renal					
Creatinine (mg/dL)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9	>5.0
(μmol/L)	<110	110–170	171–299	300–440	>440
or urine output				or <500 mL/day	or <200 mL/day

epi, epinephrine; norepi, norepinephrine.
[a]Adrenergic agents administered for at least 1 hr (doses given are in μg/kg/min).
To convert torr to kPa, multiply the value by 0.1333.

Presented below are data on the SOFA scores between treatment groups at baseline. Baseline SOFA scores are the same for both treatment groups.

Table 9. Baseline SOFA scores

SOFA Mean score	rhAPC	Placebo
Cardiovascular	3	3
Respiratory	3	3
Renal	1	1
Hematology	1	1
Hepatic	1	1

[3] Vicent et al. Crit Care Med 1998;26:1793-1800

Infection data

The lung and the abdomen were the most common site of infection. Gram-negative and gram-positive data appear in the table below.

Table 10. Baseline distribution of infection data

Variable	rhAPC (850) N (%)	Placebo (840) N (%)	Total N (1690) N (%)
Presumed Site of Infection			
Blood	45 (5)	42 (5)	87 (5)
Bone/Joint	3 (0)	8 (1)	11 (1)
Cardiac	6 (1)	3 (0)	9 (1)
CNS	20 (2)	19 (2)	39 (2)
Gynecologic	4 (1)	4 (1)	8 (1)
Head/EENT	4 (1)	4 (1)	8 (1)
Intra-Abdominal	170 (20)	167 (20)	337 (20)
Lung	456 (54)	450 (54)	906 (54)
Other	20 (2)	15 (2)	35 (2)
Pleural	5 (1)	8 (1)	13 (1)
Skin/skin structure	23 (3)	28 (3)	51 (3)
Urinary Tract	85 (10)	86 (10)	171 (10)
Vascular Catheter	9 (1)	6 (1)	15 (1)
Reason Presumed or Known			
Chest X-ray	381 (45)	376 (45)	757 (45)
Other	31 (4)	40 (5)	71 (4)
Polymorphs	24 (3)	33 (4)	57 (3)
Positive Culture/Gram	199 (23)	183 (22)	382 (23)
Underlying Disease/condition	57 (7)	51 (6)	108 (6)
Visual Inspection	158 (19)	157 (19)	315 (19)
At least 1 positive bacterial pathogen culture			
No	285 (34)	271 (32)	556 (33)
Unknown	3 (0)	2 (0)	5 (0)
Yes	562 (66)	567 (68)	1129 (67)
At least 1 positive blood culture			
No	572 (67)	567 (68)	1139 (67)
Yes	278 (33)	273 (33)	551 (33)
Type of Gram stain class of bacterial pathogen cultured			
Mixed Gram	133 (16)	117 (14)	250 (15)
No bacterial Expo	285 (34)	271 (32)	556 (33)
Pure Gram Negative	185 (22)	196 (23)	381 (23)
Pure Gram Positive	219 (26)	211 (25)	430 (25)
Unconfirm Gram	28 (3)	45 (5)	73 (4)
At least 1 positive anaerobic culture pathogen			
Mixed Aerorobic/Anaerobic	37 (4)	32 (4)	69 (4)
No bacterial Expo	285 (34)	271 (32)	556 (33)
Pure Aerobic	482 (57)	485 (58)	967 (57)
Pure Anaerobic	16 (2)	6 (1)	22 (1)
Unconfirm Aerobic/Anaerobic	30 (4)	46 (6)	76 (5)

At least 1 positive fungal culture			
No	772 (91)	767 (91)	1539 (91)
Unknown	6 (1)	9 (1)	15 (1)
Yes	72 (9)	64 (8)	136 (8)
At least 1 positive viral culture			
No	838 (99)	827 (99)	1665 (99)
Unknown	9 (1)	11 (1)	20 (1)
Yes	3 (0)	2 (0)	5 (0)
At least 1 positive parasitic culture			
No	840 (99)	829 (99)	1669 (99)
Unknown	9 (1)	11 (1)	20 (1)
Yes	1 (0)	0	1 (0)
At least 1 pathogen			
No	265 (31)	254 (30)	519 (31)
Yes	585 (69)	586 (70)	1171 (69)

CNS=Central nervous system. EENT=Eye, ear, nose throat. Pos=Positive.

Solicited patient history

Table 11. Baseline distribution of solicited patient history

Variable	rhAPC (850) N (%)	Placebo (840) N (%)	Total N (1690) N (%)
Hypertension			
No	503 (59)	530 (63)	1033 (61)
Unknown	22 (3)	16 (2)	38 (2)
Yes	325 (38)	294 (35)	619 (37)
Myocardial Infarction			
No	725 (85)	698 (83)	1423 (84)
Unknown	22 (3)	21 (3)	43 (3)
Yes	103 (12)	121 (14)	224 (13)
Congestive Cardiomyopathy			
No	770 (91)	749 (89)	1519 (90)
Unknown	26 (3)	15 (2)	41 (2)
Yes	54 (6)	76 (9)	130 (8)
Diabetes			
No	662 (78)	642 (76)	1304 (77)
Unknown	12 (1)	10 (1)	22 (1)
Yes	176 (21)	188 (22)	364 (22)
Pancreatitis			
No	803 (95)	791 (94)	1594 (94)
Unknown	18 (2)	16 (2)	34 (2)
Yes	29 (3)	33 (4)	62 (4)
Chronic Liver Disease			
No	814 (96)	803 (96)	1617 (96)
Unknown	18 (2)	15 (2)	33 (2)
Yes	18 (2)	22 (3)	40 (2)
COPD			
No	637 (75)	605 (72)	1242 (74)
Unknown	24 (3)	16 (2)	40 (2)
Yes	189 (22)	219 (26)	408 (24)
Malignancy			
No	680 (80)	663 (79)	1343 (80)
Unknown	25 (3)	19 (2)	44 (3)
Yes	145 (17)	158 (19)	303 (18)
Recent Trauma			
No	808 (95)	792 (94)	1600 (95)
Unknown	14 (2)	5 (1)	19 (1)
Yes	28 (3)	43 (5)	71 (4)
Recent Surgery			
No	597 (70)	580 (69)	1177 (70)
Unknown	8 (1)	3 (0)	11 (1)
Yes	245 (29)	257 (31)	502 (30)

COPD=Chronic Obstructive Pulmonary Disease. Recent=Within 30 days.

The table above presents data on the solicited patient history. The minor differences between the rhAPC and placebo group are shown. Of note, slightly more rhAPC treated patients had hypertension, but slightly more placebo patients had myocardial infarction, COPD, diabetes, liver disease, malignancy, recent surgery, etc.

Reviewer's comment: There are slight imbalances favoring rhAPC in several different subgroups.

Presented below are data on the recent surgical history of patients. Both treatment groups are well-balanced.

Table 12. Demographics: recent surgical history

	rhAPC (850) (%)	Placebo (840) (%)
Elective surgery	6	6
Emergency surgery	21	21
No history of history	74	73

Central laboratory data

Presented below is a summary of the baseline Protein C activity and deficiency and other laboratory biomarkers in patients.

The total number of patients that were Protein C deficient at baseline was 82%. There were patients classified as "unknown" due to an error in the sampling collection, and therefore baseline central laboratory data were not available for all patients.

Table 13. Baseline distribution of central laboratory data

Variable (Baseline)	rhAPC (850) N (%)	Placebo (840) N (%)	Total N (1690) N (%)
Protein C Activity			
=40%	330 (39)	285 (34)	615 (36)
>80%	90 (11)	105 (13)	195 (12)
Unknown	51 (6)	65 (8)	116 (7)
41-60%	240 (28)	227 (27)	467 (28)
61-80%	139 (16)	158 (19)	297 (18)
Protein C Deficiency			
Deficient	709 (83)	670 (80)	1379 (82)
Not deficient	90 (11)	105 (13)	195 (12)
Unknown	51 (6)	65 (8)	116 (7)
Severe Protein C Deficiency			
Not severely deficient	183 (22)	210 (25)	393 (23)
Severely deficient	616 (73)	565 (67)	1181 (70)
Unknown	51 (6)	65 (8)	116 (7)
ATIII Quartile			
1 (<0.44)	212 (27)	186 (24)	398 (26)
2 (0.45-0.59)	202 (25)	191 (25)	393 (25)
3 (0.60-0.74)	182 (23)	188 (25)	370 (24)
4 (=0.75)	198 (25)	199 (26)	397 (26)
Unknown	56	76	132
ATIII Deficiency			
Deficient	655 (83)	618 (81)	1273 (82)
Not deficient	139 (18)	146 (19)	285 (18)
Unknown	56	76	132
APC resistance factor V Leiden			
Negative	768 (96)	768 (96)	1536 (96)
Positive	33 (4)	32 (4)	65 (4)
Unknown	49	40	89
APC resistance factor V Hong Kong			
Negative	794 (100)	785 (100)	1579 (100)
Positive	1 (0)	2 (0)	3 (0)
Unknown	55	53	108

Protein C activity classes were defined as =40%, 41-60%, 61-80%, >80% and unknown. Protein C deficiency and severe Protein C deficiency were defined as =80% and =65% respectively. Antithrombin deficiency is described as <80% and given as percentages. Factor V Leiden or Hong Kong/Cambridge mutation for APC resistant status was described as negative or positive.

The mean platelets levels at baseline were similar with 197 x $10^3/mm^3$ in rhAPC and 204 x $10^3/mm^3$ (total mean 200 x $10^3/mm^3$) in the placebo treatment group.

Section IIIB-EFFICACY

Primary Efficacy Analysis: 28 Day All Cause Mortality and Treatment Effect

The observed mortality in all randomized patients for the ITT population is presented in the table below.

The 28 day all cause mortality in the placebo group was 31% (259/840) as compared with 25% (210/850) in the rhAPC group. This 6% reduction in mortality in rhAPC treated patients is statistically significant (p=0.0054, stratified, CMH; p=0.0049, nonstratified Chi squared). The estimate of relative risk is 0.8 [95% confidence intervals (CI): 0.7, 0.9].

Table 14. Primary 28-day all-cause mortality in all randomized patients-ITT population

THERAPY	Alive at Day 28	Died by Day 28	Total
	N (%)	N (%)	
Placebo	581 (69)	259 (**31**)	840
rhAPC	640 (75)	210 (**25**)	850
			1690

p=0.0054 (stratified, CMH); p=0.0049 (non stratified, Chi square)

Presented below is the Kaplan-Meier survival curve for all patients in the study (n=1690, ITT).

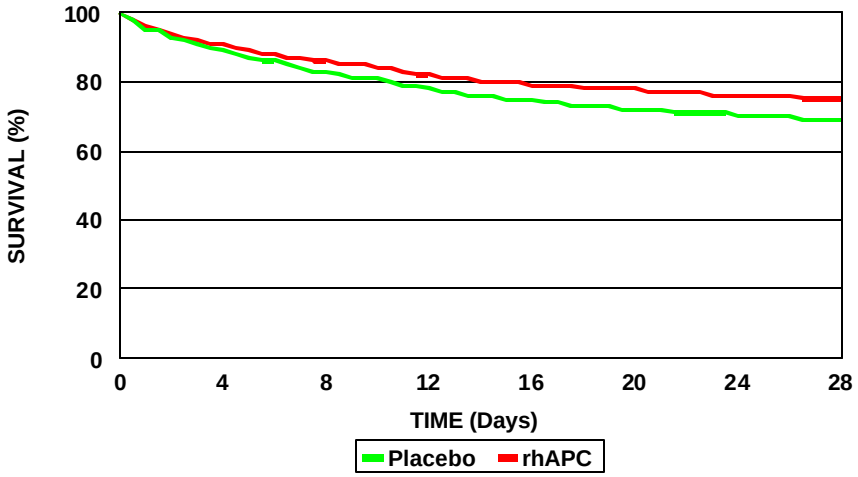


Figure 1. Kaplan-Meier survival curve for all patients

The survival curve was lower for patients in the placebo treatment group as compared to the rhAPC treatment group. The two curves separate gradually over the duration of the study. The difference between the two survival curves was statistically significant (p=0.0059, Log-Rank Test).

Treatment Effect and Gender

Below are data presented on mortality and gender of the patients.

Table 15. 28-day all-cause mortality analyses stratified by gender

Gender	rhAPC (850)		Placebo (840)		Relative	95% CI
	Total N	N (%)	Total N	N (%)	Risk (RR)	for RR
Female	373	94 (25)	353	108 (31)	0.82	0.65, 1.04
Male	477	116 (24)	487	151 (31)	0.78	0.64, 0.96

CI=Confidence Interval.

Both genders experience similar rhAPC mortality benefits.

Treatment Effect and Ethnic Origin

Below are data presented on mortality and ethnic origin of the patients.

Table 16. 28-day all-cause mortality analyses by ethnic origin

Ethnic Origin	rhAPC (850)		Placebo (840)		Relative	95% CI
	Total N	N (%)	Total N	N (%)	Risk (RR)	for RR
African descent	70	19 (27)	61	23 (38)	0.72	0.44, 1.19
Western Asian	5	0	6	1 (17)	0.39	0.02, 7.88
Caucasian	695	170 (24)	689	214 (31)	0.79	0.66, 0.94
East/South-east Asian	9	2 (22)	13	4 (31)	0.72	0.17, 3.14
Hispanic	34	7 (21)	40	8 (20)	1.03	0.42, 2.55
Other	37	12 (32)	31	9 (29)	1.12	0.54, 2.30

The mortality rates by ethnic origin do not indicate differences. The numbers are too small outside the Caucasian group to exclude differences.

Treatment Effect and Age Class

The data for mortality and age class are presented in Table 17.

Table 17. 28-day all-cause mortality analyses by age class

Age Class (years)	rhAPC (850)		Placebo (840)		Relative Risk (RR)	95% CI for RR
	Total N	N (%)	Total N	N (%)		
<60	375	59 (16)	366	75 (20)	0.77	0.56, 1.05
=60	475	151 (32)	474	184 (39)	0.82	0.69, 0.97
<65	437	68 (16)	449	94 (21)	0.74	0.56, 0.99
=65	413	142 (34)	391	165 (42)	0.81	0.68, 0.97
<75	645	141 (22)	659	170 (26)	0.85	0.70, 1.03
=75	205	69 (34)	181	89 (49)	0.68	0.54, 0.87

There appears to be a rhAPC treatment effect regardless of age. Safety data with regard to age as described in the safety section showed no trends with serious bleeds or serious adverse events.

FDA exploratory analyses included a further breakdown of age groups into intervals of 10 years to look more specifically at the mortality within different age intervals. The table below presents the efficacy outcome measures in these various age groups.

Table 18. Primary 28-day all-cause mortality analyses stratified by age

STRATA	THERAPY	Alive at Day 28	Died by Day 28	Total
		N (%)	N (%)	
AGE >10 – 20	Placebo	7 (100)	0 (0)	7
	rhAPC	8 (89)	1 (11)	9
				16
AGE >20 – 30	Placebo	36 (86)	6 (14)	42
	rhAPC	39 (89)	5 (11)	44
				86
AGE >30 – 40	Placebo	53 (85)	9 (15)	62
	rhAPC	64 (86)	10 (14)	74
				136
AGE >40 – 50	Placebo	94 (83)	19 (17)	113
	rhAPC	90 (87)	14 (13)	104
				217
AGE >50 – 60	Placebo	101 (71)	41 (29)	142
	rhAPC	115 (80)	29 (20)	144
				286
AGE >60 – 70	Placebo	124 (69)	57 (31)	181
	rhAPC	130 (74)	45 (26)	175
				356
AGE >70 – 80	Placebo	134 (61)	86 (39)	220
	rhAPC	149 (65)	82 (36)	231
				451
AGE >80 – 90	Placebo	30 (43)	39 (57)	69
	rhAPC	41 (68)	19 (32)	60
				129
AGE >90 – 100	Placebo	2 (50)	2 (50)	4
	rhAPC	4 (44)	5 (56)	9
				13
				1690

p=0.0043 (stratified, CMH). p=0.601 (heterogeneity, Breslow-Day)

A graphical representation of these data is displayed in the figure below. The number of patients (n) are shown in brackets.

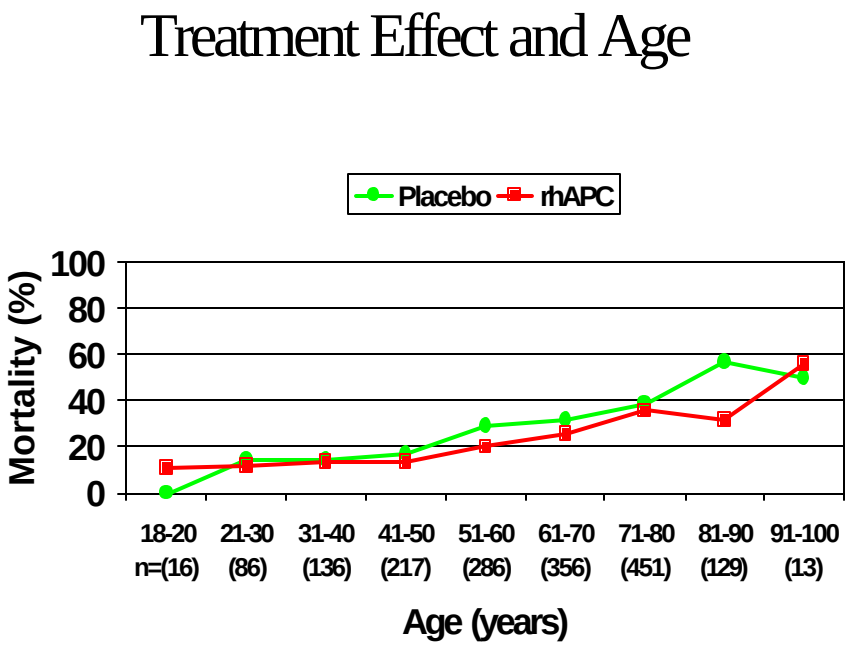


Figure 2. Mortality by age intervals of approximately ten years

Reviewer comment: Overall, mortality tends to increase with age. The data suggest benefit appeared to be higher among patients > 50 years of age compared to younger patients. At each ends of the curves, there are small numbers of patients.

Treatment Effect and Baseline APACHE II Score

The Acute Physiology and Chronic Health Evaluation (APACHE) II[4] was used in this study. It is a classification system that assesses a patient's severity of disease based on 12 physiologic measurements, age, and previous health status. The higher the APACHE II score, the greater the severity of disease involvement. Below is the APACHE II scoring system.

APACHE II Scoring System

A Acute Physiology Points:

	High Abnormal Range					Low Abnormal Range			
Physiologic variable	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature (rectal, °C)	≥41	39-40.9		38.5-38.9	36- 38.4	34-35.9	32 -33.9	30 -31.9	≤29.9
Mean Arterial Pressure (mm Hg)	≥160	130 – 155	110-129		70-109		50-69		≤49
Heart rate (ventricular response)	≥ 180	140-179	110-139		70-109		55-69	40-54	≤39
Respiratory rate (non-ventilated orientation)	≥50	35-49		25-34	12-24	10-11	6-9		≤5
Oxygenation: $AaDO_2$ or PaO_2 (mmHg) a. FIO_2 ≥0.5 record only AaDO b. FIO_2 <0.5 record only PaO_2	≥500	350-499	200-349		<200 PO_2 >70	PO_2 61-70		PO_2 55-60	PO_2 <55
Arterial pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
Serum sodium (mMd/L)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
Serum potassium (mMd/L)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
Serum creatinine (mg/100 mL) (double point score for acute renal failure.)	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
Hematocrit (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
White Blood Count	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
Glasgow Coma Score (GCS) Score = 15 minus actual GCS									
Total Acute Physiology Score									
Serum HCO_3 (venus, mMd/L) (not preferred, use if no ABGs)	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15

B AGE POINTS:

Assign points to age as follows:

Age (yrs)	Points
≥ 44	0
45 – 54	2
56 – 64	3
65 – 74	5
≤ 75	6

C CHRONIC HEALTH POINTS:

If the patient has a history of severe organ insufficiency or is immunocompromised, assign points as follows:

a. nonoperative or emergency post-operative patients: 5 points
b. elective postoperative patients: 2 points

Definitions: Organ insufficiency or immunocompromised state evident prior to this hospital admission and conforming to the following criteria:
LIVER: Biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma.
CARDIOVASCULAR: New York Heart Association Class IV.
RESPIRATORY: Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, ie, unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mm Hg), or respirator dependency.
RENAL: Receiving chronic dialysis.
IMMUNOCOMPROMISED: Patient has received therapy that suppresses resistance to infection, eg, immunosuppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection (eg, leukemia, lymphoma, AIDS)

APACHE II SCORE

Sum of A + B + C

A APS Points _____
B Age Points _____
C Chronic Health Points _____

TOTAL APACHE II _____

[4] Knaus WA 1985; 13:818-829.

The APACHE II scores were divided into quartiles. The scores in the APACHE II quartiles ranged from 3-19, the second from 20-24, the third from 25-29 and finally the fourth from 30-53.

Presented below are data on interactions between APACHE II scores and mortality. These data show some evidence of an interaction between treatment effect, mortality and APACHE II quartiles; p=0.09 for the interaction.

Table 19. 28-day all-cause mortality analyses by APACHE II quartiles

APACHE II Quartile (score)	rhAPC (850)		Placebo (840)		Mort diff (%)	RR	95% CI for RR
	Total N	N (%)	Total N	N (%)			
1st (3-19)	218	33 (15)	215	26 (12)	+3	1.25	0.78, 2.02
2nd (20-24)	218	49 (22)	222	57 (26)	-4	0.88	0.63, 1.22
3rd (25-29)	204	48 (24)	162	58 (36)	-12	0.66	0.48, 0.91
4th (30-53)	210	80 (38)	241	118 (49)	-11	0.78	0.63, 0.96

Reviewer comment: In contrast to the all the other quartiles, the mortality for patients in the first quartile who receive rhAPC is higher than for patients on placebo, 15 vs. 12% respectively, and the relative risk is 1.25. This reverse trend in mortality is of concern, particularly due to the significant number of serious bleeds, which occurred in the APACHE II first quartile. Safety data for the first APACHE II quartile are presented under the safety section. The observation that the treatment effect was smaller in the second quartile than in the third and fourth quartiles together with the observation that it was reversed in the first quartile raises the question of whether the treatment has benefit in patients with lower APACHE II scores. Potentially the serious bleeding events may have an adverse effect on survival, which overrides any benefit in the less severely ill patients. The mortality differences between rhAPC and placebo arms tend to increase with the quartile. The largest rhAPC effects are seen in the 3rd and 4th quartiles. The relative risks also suggest the greatest rhAPC benefit in the 3rd and 4th quartiles.

Table 20. 28-day all-cause mortality for all patients and for subgroups defined by APACHE II as a measure of disease severity

	rhAPC Total N	rhAPC N (%)	Placebo Total N	Placebo N (%)	Absolute Mort diff (%)	RR	95% CI for RR
Overall	850	210 (24.7)*	840	259 (30.8)	-6.1	0.81	0.70, 0.93
Apache II quartile (score)							
1st + 2nd (3-24)	436	82 (19)	437	83 (19)	0	0.99	0.75, 1.30
3rd + 4th (25-53)	414	128 (31)	403	176 (44)	-13	0.71	0.59, 0.85

*P-value for difference between rhAPC and placebo was 0.005, CMH, stratified by baseline APACHE II, age, and baseline protein C.

Reviewer comment: Comparisons of the rhAPC treated effect in patients above and below the median reveal that all the rhAPC mortality benefit was seen in patients who presented with APACHE II scores =25.

Presented below are the Kaplan-Meier survival curves for APACHE II quartiles.

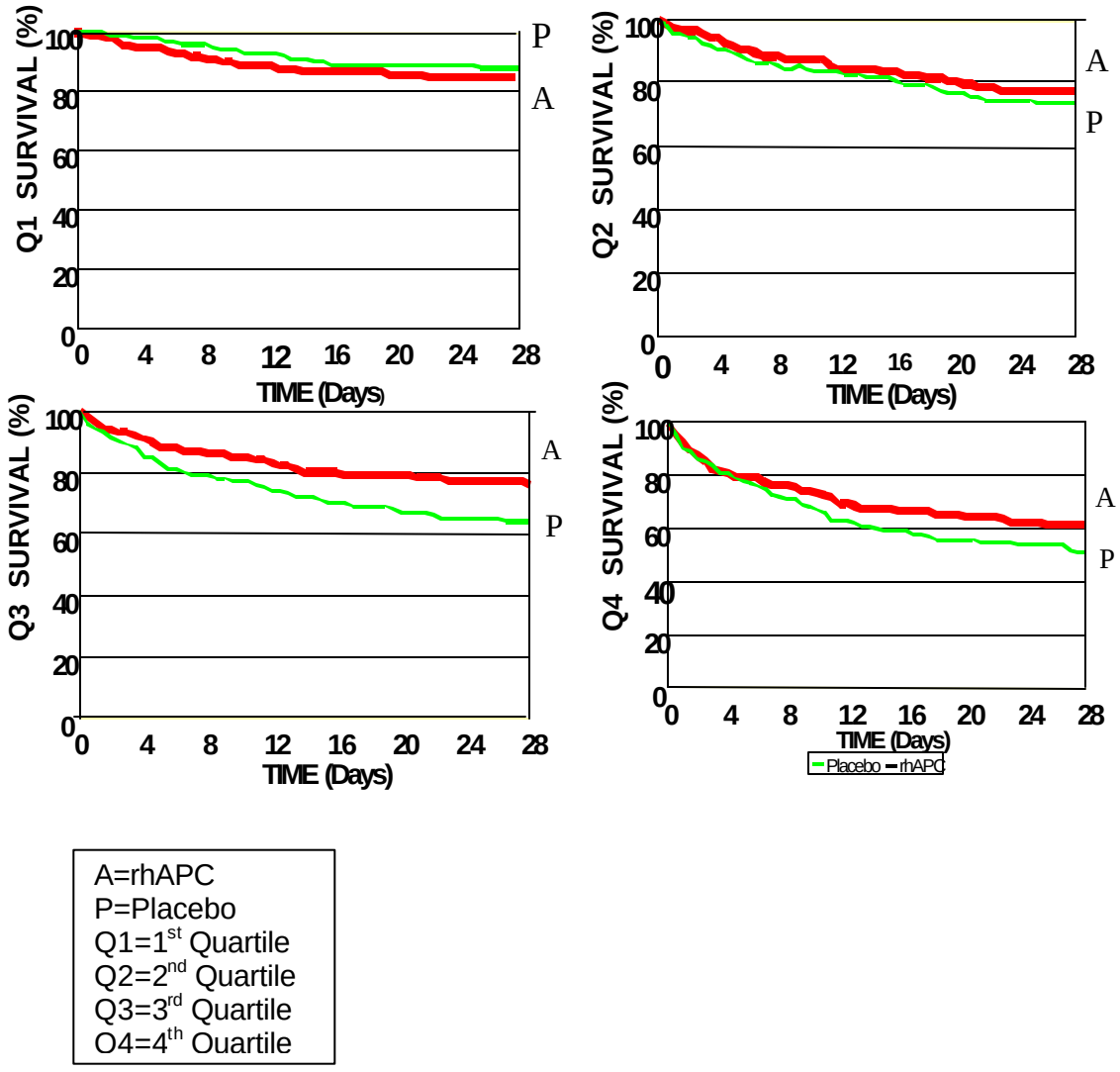


Figure 3. Kaplan-Meier survival curves as a function of APACHE II quartiles

Reviewer comment: Among patients in the first quartile, survival was slightly higher in patients randomized to placebo than rhAPC. Note that in the fourth quartile, the curves separated later than in the third quartile.

These interactions between treatment and baseline APACHE II scores were further analyzed by dividing baseline APACHE II scores into intervals of 5 units. These results are presented in the table below.

Table 21. Primary 28-day all-cause mortality analyses stratified by APACHE II score at baseline

STRATA	THERAPY	Alive at Day 28	Died by Day 28	Total
		N (%)	N (%)	
APACHE II Score 0-5	Placebo	1 (100)	0 (0)	1
	rhAPC	1 (100)	0 (0)	1
				2
APACHE II Score >5-10	Placebo	12 (92)	1 (8)	13
	rhAPC	9 (82)	2 (18)	11
				24
APACHE II Score >10-15	Placebo	64 (86)	10 (14)	74
	rhAPC	68 (87)	10 (13)	78
				152
APACHE II Score >15-20	Placebo	135 (84)	26 (16)	161
	rhAPC	140 (83)	29 (17)	169
				330
APACHE II Score >20 - 25	Placebo	169 (75)	55 (25)	224
	rhAPC	178 (77)	54 (23)	232
				456
APACHE II Score >25 - 30	Placebo	98 (61)	62 (39)	160
	rhAPC	142 (77)	43 (23)	185
				345
APACHE II Score >30-35	Placebo	63 (54)	54 (46)	117
	rhAPC	68 (62)	42 (38)	110
				227
APACHE II Score >35-40	Placebo	27 (42)	38 (58)	65
	rhAPC	21 (57)	16 (43)	37
				102
APACHE II Score >40-45	Placebo	10 (53)	9 (47)	19
	rhAPC	9 (50)	9 (50)	18
				37
APACHE II Score >45-50	Placebo	2 (33)	4 (67)	6
	rhAPC	3 (43)	4 (57)	7
				13
APACHE II Score >50-55	Placebo	0	0	0
	rhAPC	1 (50)	1 (50)	2
				2
				1690

p=0.0142 (stratified, CMH), p=0.403 (heterogeneity, Breslow-Day)

Reviewer comment: The treatment effect appears to occur largely in patients with APACHE II scores > 25.

A graphical representation of these data is presented in the below figure. The number of patients (n) is shown in brackets.

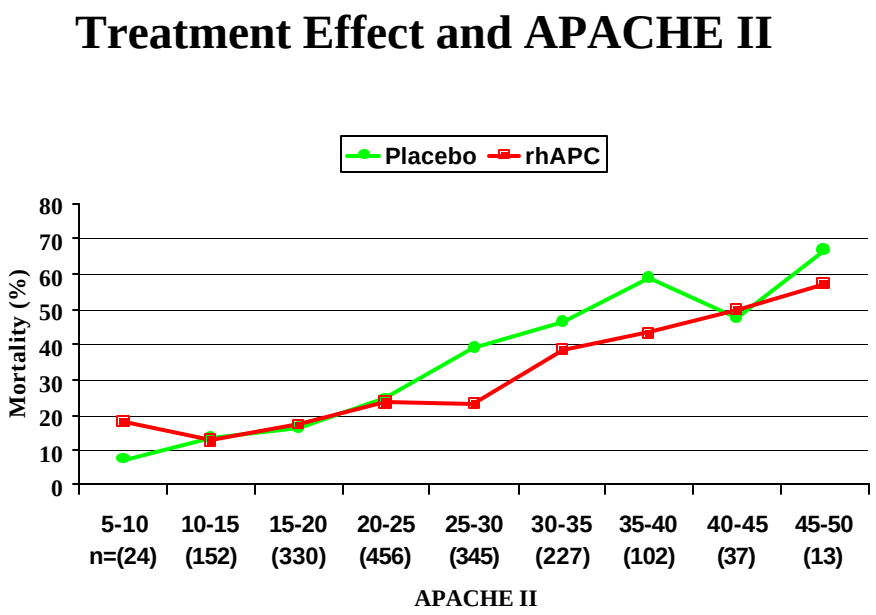
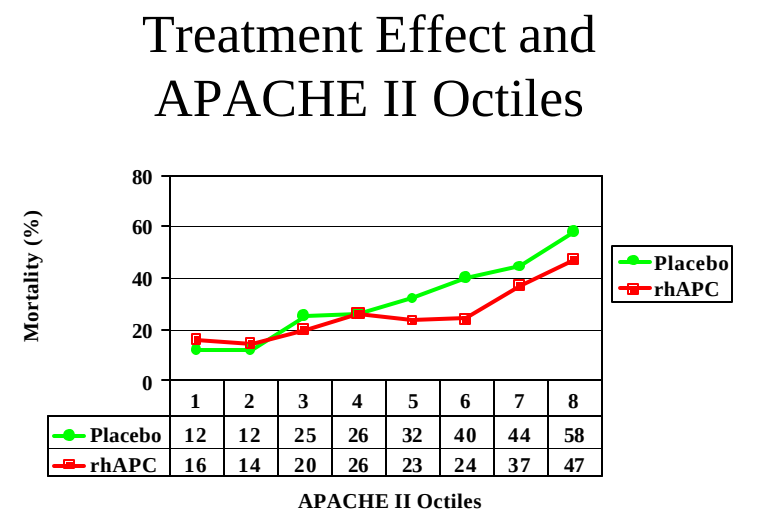


Figure 4. Mortality by APACHE II intervals of 5 units

Reviewer comment: There is no separation between the curves with APACHE II below 25. As can be seen in the above figure, only after an APACHE II score of 25 do the curves begin to separate showing clear treatment benefit. At both ends of the curves there are few patients so little can be made of these data.

FDA exploratory analyses included a further breakdown of APACHE II scores into finer intervals, APACHE II octiles and half octiles, as shown in the below figure.



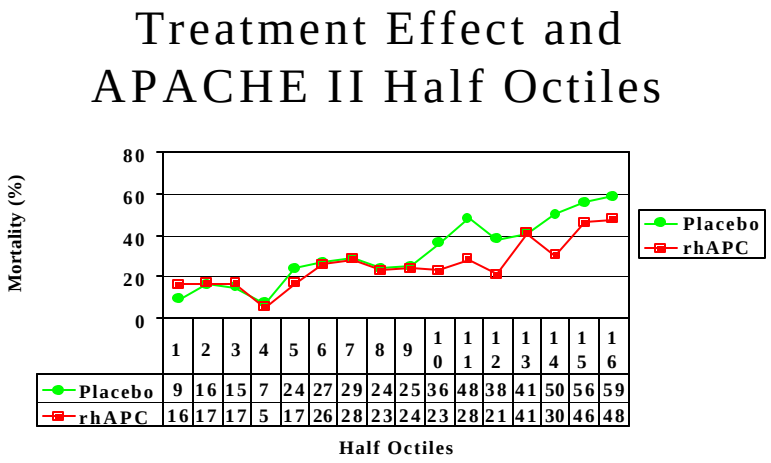


Figure 5. Treatment effect by APACHE II octiles and half octiles

Reviewer comment: A similar trend was observed. The curves do not appear to separate initially, however, a clear separation occurs with APACHE II scores > 25.

Reviewer comment: The hypothesis, generated from these prospective analyses, that rhAPC efficacy may differ as a function of baseline mortality risk was assessed for strength and consistency of evidence as well as biological plausibility, leading to a determination that the efficacy of rhAPC had not been established in patients with lower risk of mortality, e.g., APACHE II score < 25.

FDA analyses further explored chronic APACHE II health points to examine whether sicker patients experienced greater treatment benefit. Chronic APACHE II health points are a component of the APACHE II score. They are assigned to patients with rather severe underlying diseases predating the acute illness.

Chronic health points indicate whether the patient has a history of severe organ insufficiency or is immunocompromised. Organ insufficiency or immunocompromised state was defined as the state evident prior to hospital admission and the following: liver-biopsy proven cirrhosis and documented portal hypertension, or prior episode of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma; cardiovascular-New York Heart Association class IV; respiratory-chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, i.e. unable to climb stairs or perform household duties, or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (40 mm Hg) or respiratory dependency; renal-receiving chronic dialysis; immunocompromised-patient has received therapy that suppress resistance to infection, eg. immunosuppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection eg. leukemia, lymphoma, AIDS. With chronic APACHE II health points, patients are assigned a score of 0, 2 and 5 (5 points-nonoperative or emergency post-operative patients; 2 points-elective postoperative patients).

Presented below are data on mortality with APACHE II chronic health points.

Table 22. Mortality by combined APACHE II chronic health points

Chronic Health Points	rhAPC	Placebo
0	163/681 (24%)	176/664 (27%)
>0	47/169 (28%)	83/176 (47%)

Reviewer comment: In patients with chronic APACHE II health points, there was a greater treatment effect compared to patients without any chronic health points.

Treatment Effect and Organ Failure

Presented below are data on treatment effect and the number of organ dysfunctions at baseline. Organ failures are defined under the study inclusion and exclusion criteria.

Table 23. 28-day all-cause morality subgroups analyses for number of organ failures

Number of Organ Failure	rhAPC (850) Total N	N (%)	Placebo (840) Total N	N (%)	Mort Diff (%)	Relative Risk (RR)	95% CI for RR
1	215	42 (20)	203	43 (21)	-1	0.92	0.63, 1.35
2	270	56 (21)	273	71 (26)	-5	0.80	0.59, 1.08
3	214	56 (26)	218	75 (34)	-8	0.76	0.57, 1.02
4	119	46 (39)	116	54 (47)	-8	0.83	0.62, 1.12
5	31	10 (32)	30	16 (53)	-21	0.60	0.33, 1.11

CI=Confidence Intervals.

Reviewer comment: Approximately 75% of patients had more than one organ failure at study entry. Among those with only one organ failure, mortality rates were 20% rhAPC vs. 21% placebo. When dichotomizing patients by 1 vs. 2 or more organ failures, treatment benefit appears greater in patients with 2 or more organ failures, 168/634 (26%) for rhAPC vs. 216/637 (34%) for placebo.

A graphical representation of these data are displayed in the below figure.

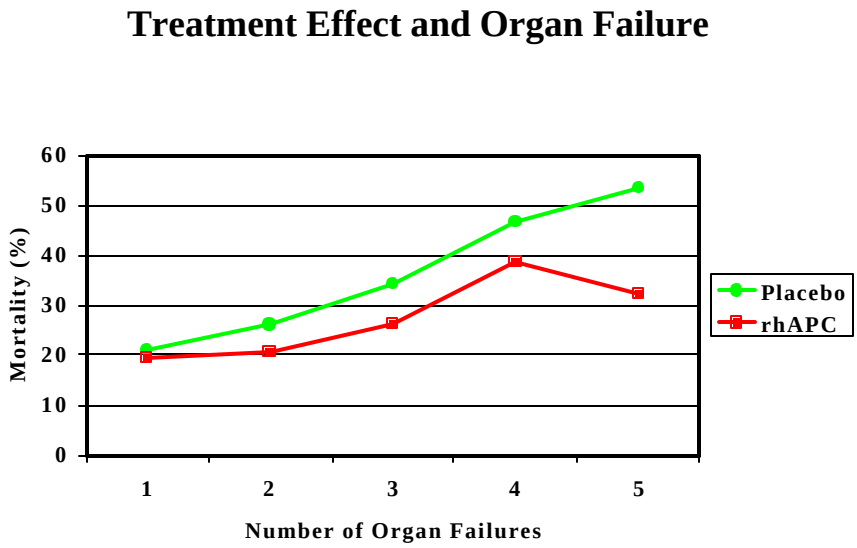


Figure 6. Mortality by number of organ failures

Patients with only 1 dysfunctional organ at baseline were less likely to have a beneficial treatment effect than were those with 2 or more dysfunctional organs.

Presented below are data on mortality and organ failures at baseline. The table below displays mortality data in the presence or absence of different organ failures at baseline.

Table 24. Primary 28-day all-cause mortality analyses stratified by the presence or absence of organ failure at baseline

STRATA Organ Failure	THERAPY	Alive at Day 28	Died by Day 28	Total
		N (%)	N (%)	
Cardiovascular: No	Placebo	165 (72)	63 (28)	228
	rhAPC	189 (76)	59 (24)	248
				476
Cardiovascular: Yes	Placebo	416 (68)	196 (32)	612
	rhAPC	451 (75)	151 (25)	602
				1214
Hematology: No	Placebo	499 (70)	211 (30)	710
	rhAPC	540 (76)	172 (24)	712
				1422
Hematology: Yes	Placebo	82 (63)	48 (37)	130
	rhAPC	100 (72)	38 (28)	138
				268
Metabolic Acidosis: No	Placebo	416 (75)	142 (25)	558
	rhAPC	430 (78)	121 (22)	551
				1109
Metabolic Acidosis: Yes	Placebo	165 (59)	117 (41)	282
	rhAPC	210 (70)	89 (30)	299
				581
Renal Failure: No	Placebo	371 (76)	116 (24)	487
	rhAPC	399 (81)	94 (19)	493
				980
Renal Failure: Yes	Placebo	210 (59)	143 (41)	353
	rhAPC	241 (68)	116 (32)	357
				710
Respiratory: No	Placebo	143 (72)	57 (29)	200
	rhAPC	170 (78)	48 (22)	218
				418
Respiratory: Yes	Placebo	438 (68)	202 (32)	640
	rhAPC	470 (74)	162 (26)	632
				1272

Reviewer comment: Treatment effects appeared relatively consistent regardless of organ dysfunction type (i.e. cardiovascular, renal, pulmonary, hematologic and acidotic dysfunctions).

The below table displays data on mortality and the first sepsis induced organ failure which occurred in the patient.

Table 25. Primary 28-day all-cause mortality analyses stratified by first sepsis induced organ failure at baseline

STRATA	THERAPY	Alive at Day 28	Died at Day 28	Total
		N (%)	**N (%)**	
Cardiovascular	**Placebo**	178 (74)	63 (26)	241
	rhAPC	206 (82)	45 (18)	251
				492
Hematology	**Placebo**	23 (64)	13 (36)	36
	rhAPC	27 (75)	9 (25)	36
				72
Metabolic Acidosis	**Placebo**	37 (58)	27 (42)	64
	rhAPC	46 (73)	17 (27)	63
				127
Renal	**Placebo**	41 (66)	21 (34)	62
	rhAPC	52 (69)	23 (31)	75
				137
Respiratory	**Placebo**	246 (72)	96 (28)	342
	rhAPC	239 (73)	88 (27)	327
				669
Multiple Organ	**Placebo**	56 (59)	39 (41)	95
	rhAPC	69 (71)	28 (29)	97
				192
				1689[5]

Reviewer comment: Regardless of what type of organ failure occurred first, mortality was lower in the rhAPC group than placebo.

[5] Data from one patient not available.

Treatment Effect in Subgroups Defined by Organ Failure and APACHE II Quartiles

Presented below are data on the observed mortality in the twenty subgroups defined by organ failure and APACHE II quartiles.

Table 26. Observed mortality in strata defined by APACHE II quartiles and number of organ dysfunctions at baseline

Number of organ failures at baseline		APACHE II Quartile							
		First		Second		Third		Fourth	
		%	N	%	N	%	N	%	N
1	Placebo	8	77	25	61	15	34	55	31
	rhAPC	7	89	22	59	29	38	41	29
2	Placebo	16	80	23	77	40	48	31	68
	rhAPC	13	75	22	81	18	61	32	53
3	Placebo	13	40	21	53	43	47	50	78
	rhAPC	31	39	23	52	20	60	32	63
4	Placebo	12	17	44	25	38	29	67	45
	rhAPC	36	14	20	20	37	35	48	50
5	Placebo	0	1	33	6	75	4	58	19
	rhAPC	0	0	33	6	10	10	47	15

The shaded strata show groups with relative risks on rhAPC less than 0.8 than on placebo.

Reviewer comment: As observed by the shaded strata, relative risks of less than 0.8 tend to occur in the higher APACHE II quartiles regardless of the number of dysfunctional organs.

Presented below are data on mortality within the first APACHE II quartile by number of organ failures. This analysis was conducted to further examine the patient population within the first APACHE II quartile as the mortality in the first APACHE II quartile was greater on rhAPC vs. placebo compared to the other APACHE II quartiles.

Table 27. Mortality within first APACHE II quartile by number of organ failures

Number of organ failures (OF)	rhAPC		Placebo		RR
	N	N (%)	N	N (%)	
< 3 OF (322)	165	16 (10)	157	19 (12)	0.80
= 3 OF (111)	53	17 (32)	58	7 (12)	2.66

OF=organ failure.

Reviewer comment: This analysis shows mortality is greater among patients in the first APACHE II quartile with rhAPC vs. placebo when there are 3 or more organ failures. Thus, the number of organ failures appears not to be as good a predictor of response to rhAPC than does APACHE II.

A further analysis was performed by the mortality within the first APACHE II quartile and number of organ failures and chronic APACHE II health points. This was to examine whether this subgroup had chronic illness, i.e., chronic health points.

Table 28. Mortality within first APACHE II quartile by number of organ failures and APACHE II chronic health points

	Chronic Health Points					
	0		**2**		**5**	
	Total N	N (%)	Total N	N (%)	Total N	N (%)
< 3 Organ Failures						
rhAPC	152	16 (11)	1	0 (0)	12	0 (0)
Placebo	150	17 (11)	3	0 (0)	4	2 (50)
= 3 Organ Failures						
rhAPC	51	16 (31)	1	0 (0)	1	1 (100)
Placebo	55	7 (13)	1	0 (0)	2	0(0)

Reviewer comment: The analysis above reveals few patients in the first APACHE II quartile had chronic APACHE II health points.

Treatment Effect and Protein C Levels

Presented below are data on mortality and amount of Protein C activity present at baseline in patients.

Table 29. 28-day all-cause mortality analyses stratified by Protein C activity class

Protein C Activity Class	rhAPC		Placebo		Relative Risk	95% CI for RR
	Total N	N (%)	Total N	N (%)		
Unknown	51	14 (28)	65	16 (25)	1.12	0.60, 2.07
= 40%	330	91 (28)	285	119 (42)	0.66	0.53, 0.82
41-60%	240	65 (27)	227	56 (25)	1.10	0.81, 1.49
61-80%	139	26 (19)	158	40 (25)	0.74	0.48, 1.14
> 80%	90	14 (16)	105	28 (27)	0.58	0.33, 1.04

No clear trends were noted with mortality and Protein C activity. Mortality was greater on rhAPC in the unknown and 41-60% class. Due to a sampling error not all laboratory values were available for all patients. The unknown category was the small number of patients who did not have the tests performed due to laboratory error, so it was unknown whether the patient was protein C deficient or not.

Presented below are data on mortality and the Protein C deficiency status of patients at baseline. Patients were considered to have Protein C deficiency if the levels were = 80%.

Table 30. 28-day all-cause mortality analyses by Protein C deficiency class

Protein C Deficiency	rhAPC (850)		Placebo (840)		Mort Diff (%)	Relative Risk	95% CI for RR
	Total N	Mortality N (%)	Total N	Mortality N (%)			
Deficient (= 80%)	709	182 (26)	670	215 (32)	-6	0.80	0.68, 0.95
Not deficient (> 80%)	90	14 (16)	105	28 (27)	-11	0.58	0.33, 1.04
Unknown or Absent	51	14 (27)	65	16 (25)	+2	1.12	0.60, 2.07

These data show no clear correlation between baseline protein C levels and treatment effect from rhAPC.

Reviewer comment: Relatively few patients were not protein C deficient at baseline, but there appears to be no relationship between protein C deficiency and treatment with rhAPC.

Treatment Effect and Shock

Approximately 70% of the patients were in shock within the 6-hour period preceding study drug administration. In this study, patients were classified as being in shock at baseline if they met any of the following criteria for at least 1 hour despite adequate fluid resuscitation or adequate intravascular volume status at any time within the 6 hours prior to the start of study drug infusion:

- An arterial systolic blood pressure (SBP) of =90 mm Hg.
- A mean arterial pressure (MAP) of =70 mm Hg.
- The need for vasopressors to maintain SBP =90 mm Hg or MAP =70 mm Hg.

Adequate fluid resuscitation or adequate intravascular volume was defined as one or more of the following:

(a) The administration of an iv fluid bolus (500 mL of crystalloid solution, =20 g of albumin, or =200 mL of other colloids administered over 30 minutes or less).
(b) Pulmonary arterial wedge pressure greater than or equal to 12 mm Hg.
(c) Central venous pressure =8 mmHg.

Vasopressors were defined as the following:

(a) Dopamine =5 µg/kg/min.
(b) Norepinephrine, epinephrine, or phenylephrine at any dose.

Note: Dobutamine and dopexamine are not considered vasopressors.

Presented below are data showing mortality in patients with and without shock.

Table 31. Mortality and shock

Shock	rhAPC		Placebo		Mort diff	RR	95% CI
	Total N	N (%)	Total N	N (%)	(%)		for RR
No	252	53 (21)	238	53 (22)	-1	0.94	0.67, 1.32
Yes	598	157 (26)	602	206 (34)	-8	0.77	0.64, 0.91

Table 32. Mortality and vasopressor use

Vaso-	rhAPC		Placebo		Mort diff	RR	95% CI
pressors	Total N	N (%)	Total N	N (%)	(%)		for RR
No	334	70 (21)	299	78 (26)	-5	0.80	0.61, 1.07
Yes	516	140 (27)	541	181 (33)	-6	0.81	0.68, 0.98

Reviewer comment: Approximately 70% of the patients were in shock at study entry. Among patients in shock, mortality rates were 26% rhAPC vs 34% placebo, however among patients not in shock, the mortality rates were 21% rhAPC vs 22% placebo. Thus, it appears there is little benefit in the group without shock. However, as stated earlier the sponsor's definition differed from the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) guidelines. The sponsor's definition of shock is defined as the presence or absence of cardiovascular organ failure, as defined in the

inclusion criteria, with hypotension or vasopressor support within 6 hours prior to study drug administration. The definition of septic shock according to the ACCP/SCCM requires both hypotension plus evidence of end-organ perfusion. Therefore it is highly likely fewer patients would meet the definition of shock if the sponsor had used the ACCP/SCCM criteria. In order to explore more fully the effect of rhAPC in patients in shock and not in shock, a retrospective subgroup was generated of "any shock-yes or no". "Any shock-no" included patients who had no cardiovascular organ failure within 48 hours of study drug and no cardiovascular organ failure within 6 hours of study drug and a cardiovascular SOFA of less than 3 (i.e., not requiring high dose vasopressors). In other words, no cardiovascular failure by any assessment prior to the administration of study drug. Based on this post hoc definition, there appeared to be a similar rhAPC treatment effect in patients in shock and not in shock as shown in Table 32. *We assessed the treatment effect in the 633 patients not requiring high dose vasopressors within the 24 hours prior to study drug administration. The RR was (0.80, similar to that of patients requiring high dose vasopressors within the same time period (n=1057; RR=0.81). Thus, based on a post hoc analysis of subgroups considered to be more in keeping with conventional definitions of shock, a rhAPC treatment effect was observed in both shock and not-in-shock groups.*

Treatment Effect and SOFA Scores

Analyses were performed to evaluate rhAPC or placebo effects on Sequential Organ Failure Assessment (SOFA) scores. The SOFA scoring system is a 0-4 scale. The higher the score, the more severe the organ (respiratory, coagulation, liver, cardiovascular, and renal) failure assessment.

Presented below are the time-averaged SOFA scores.

Table 33. Time-averaged SOFA scores

SOFA Mean score		1-4 days	1-7 days	1-14 days	1-28 days
Cardiovascular	rhAPC	1.9	1.7	1.4	1.3
	Placebo	2.1	1.8	1.6	1.5
Respiratory	rhAPC	2.4	2.3	2.2	2.1
	Placebo	2.4	2.4	2.3	2.2
Renal	rhAPC	1.0	1.0	1.0	1.1
	Placebo	1.0	1.1	1.1	1.3
Hematology	rhAPC	1.1	1.1	1.0	1.0
	Placebo	1.2	1.1	1.1	1.1
Hepatic	rhAPC	0.8	0.9	1.0	1.1
	Placebo	0.8	0.9	1.0	1.1

Reviewer comment: No differences were observed between rhAPC and placebo in renal, hematologic and hepatic function. A reduction was observed in the time-averaged SOFA scores at various time periods for cardiovascular function between the rhAPC and placebo treatment group. There was also a favorable trend for of rhAPC on respiratory function at some of the timeframes.

The figure below is a plot of the relative risk estimates and their 95% confidence intervals (CI) across the subgroups defined by various clinical measures of disease severity.

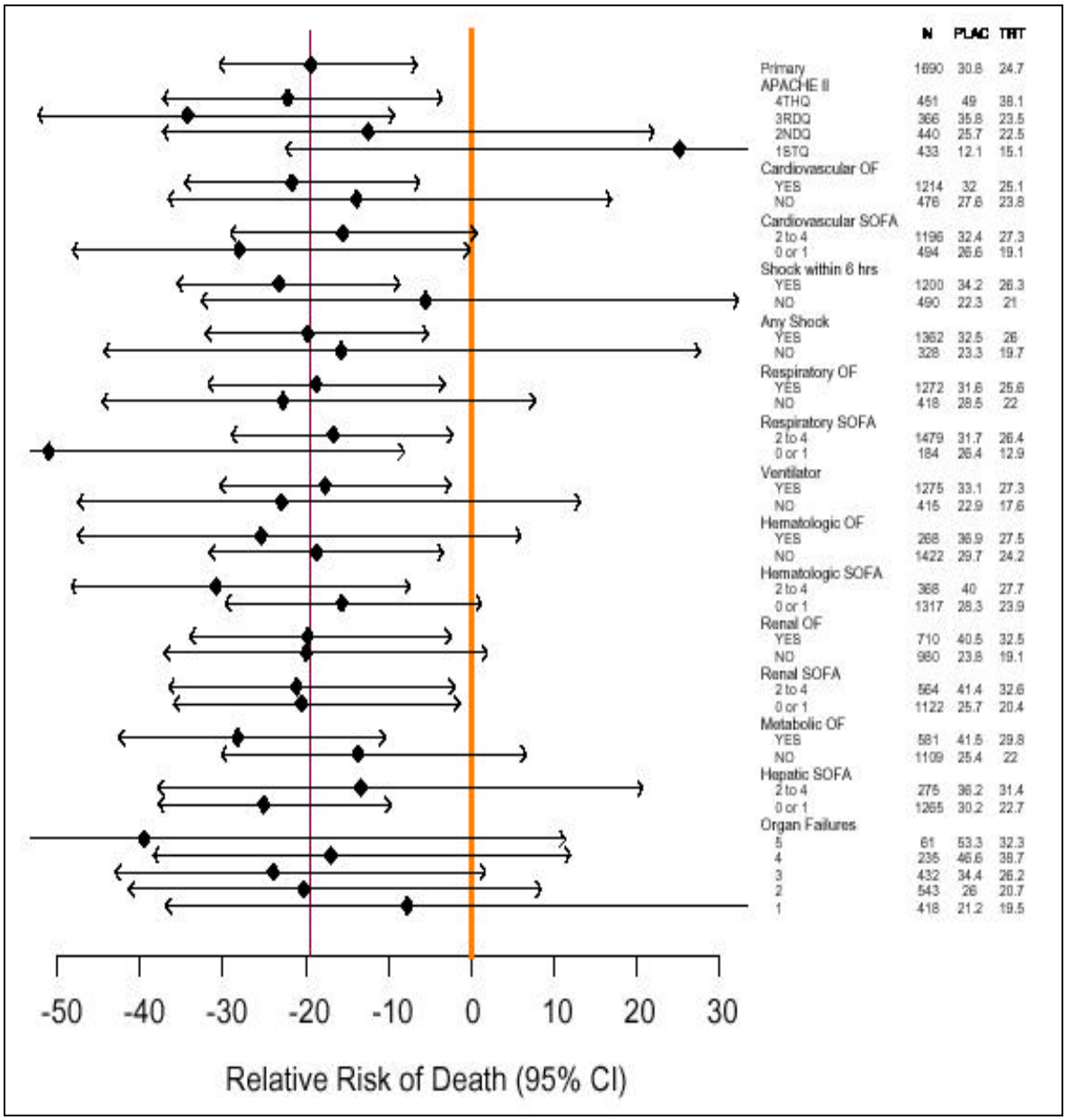


Figure 7. 28-day all-cause mortality across subgroups defined by clinical measures of baseline disease severity

The point estimates of the relative risks are shown by the diamonds below and the limits of 95% CI by the horizontal lines. If the observed mortality in rhAPC and placebo groups are the same, then the relative risk estimate is equal to one. A relative risk estimate of less than 1 indicates lower mortality in the rhAPC group compared to placebo; on the other hand, a relative risk estimate greater than 1, indicates a higher risk of mortality in the rhAPC group relative to placebo.

Presented in the figure below is a summary of mortality and the variables APACHE II, organ failure and shock. These are the same data presented in Figure 7. However, it highlights three variables of interest and is a logarithmic scale.

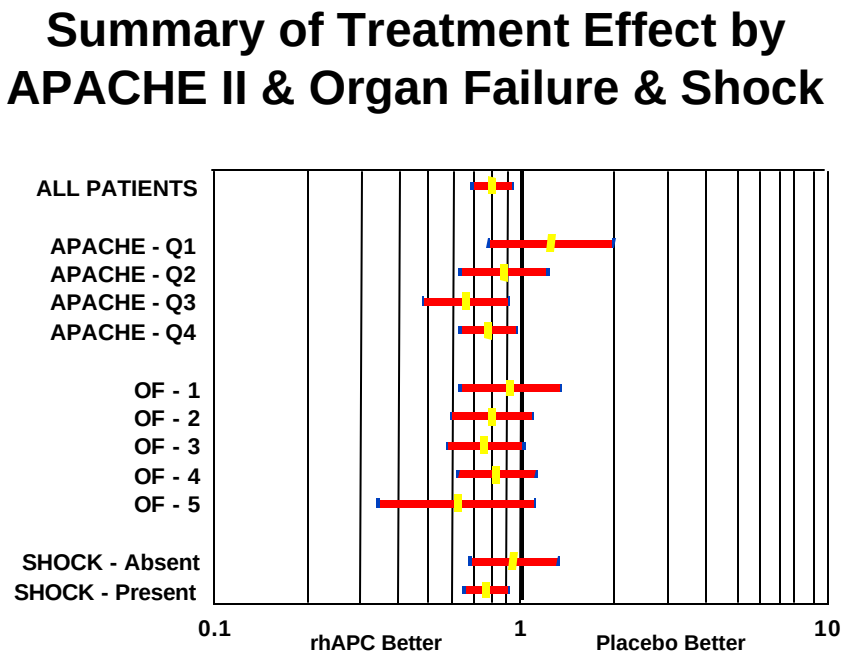


Figure 8. Summary of treatment effect by APACHE II and organ failure and shock

Reviewer comment: Figure 8 in particular highlights the discriminatory ability, based on APACHE II quartiles, to separate out those who were less likely to experience rhAPC benefit.

Treatment Effect and disseminated intravascular coagulation (DIC)

rhAPC or drotrecogin alfa (activated), has anti-thrombotic and pro-fibrinolytic properties that may contribute to its mortality effects in patients with severe sepsis. Thus, one might see different effects in patients with sepsis who have DIC from those who do not. The majority of patients in the trial (> 90%) had laboratory evidence of DIC at study entry, as defined by the presence of 2 or more of the following laboratory findings:

- platelet count <100,000/mm^3 or 50% decrease in the past three days
- PT or APTT >1.2 x ULN
- D-dimer >ULN
- Protein C, Protein S or Anti-thrombin <LLN

Reviewer comment: Of note, the sponsor's definition of DIC is inconsistent with other definitions of DIC in severe sepsis. In other trials 20-30% of the patients with severe sepsis had DIC compared with 70% who did not have DIC.

Presented below are data showing mortality in patients with DIC at baseline, as defined by the sponsor.

Table 34. Primary 28-day all-cause mortality analyses stratified by the presence of DIC at baseline

DIC Status at Baseline	rhAPC		Placebo		Relative Risk	95% CI for RR
	Total N	Mortality N (%)	Total N	Mortality N (%)		
Present	800	196 (25)	774	243 (31)	0.78	0.66, 0.92
Absent or unknown	49	14 (29)	66	16 (24)	1.18	0.64, 2.18

Reviewer comment: In 2 individuals who did not have DIC at baseline and 113 patients in whom insufficient laboratory data were available to determine DIC, there was little suggestion of a treatment effect.

There is no standardized definition of DIC. DIC is a syndrome with clinical and laboratory manifestations. The sponsor defined patients with DIC at baseline if they met 2 of 4 criteria as described above within 24 hours prior to initiating the study. Note, the sponsor's choice of Protein C, Protein S activity and antithrombin III are not routinely used in definitions of DIC that are more commonly used in clinical practice.

As a means of assessing effects of rhAPC in the context of a more traditional definition of DIC, we chose platelet count as a reasonable "surrogate" marker for DIC, since every patient had a baseline platelet count. If one considers everyone with a platelet count < 100,000 as having presumptive DIC, then approximately 30% of patients had "DIC" in PROWESS, more in keeping with other studies observed. There was a rhAPC treatment effect in the patients above and below this platelet cut off point although the differential was less pronounced in those with platelet counts > 100,000.

Table 35. Mortality and platelet counts

Platelets ($/mm^3$)	rhAPC N (%)	Placebo N (%)
= 100,000	79/278 (28)	102/266 (38)
> 100,000	131/572 (23)	157/574 (27)

Reviewer comment: Thus, if one used a platelet count criterion of less than or equal to or greater than 100,000/mm^3 as a reasonable indication of presence or absence of DIC, there appeared to be an rhAPC treatment effect in both subsets of patients.

Treatment effect and heparin use

Low Dose Heparin

Many patients received low dose heparin for prophylaxis of deep venous thrombosis. Both heparin and rhAPC have anti-thrombotic effects. Mortality was lower in patients who received rhAPC than in those receiving placebo regardless of whether low dose heparin was used, but the treatment effect was several fold greater in patients not on low dose heparin, as seen in the table below.

Table 36. Mortality and heparin use

On Heparin	rhAPC		Placebo		
	N	Mortality N (%)	N	Mortality N (%)	Mortality difference %
At baseline	532	138 (26)	559	170 (30)	-4
During infusion	634	158 (25)	637	179 (28)	-3
By day 1*	567	134 (24)	578	154 (27)	-3
Not on Heparin	rhAPC		Placebo		
	N	Mortality N (%)	N	Mortality N (%)	Mortality difference %
At baseline	318	72 (23)	281	89 (32)	-9
During infusion	216	52 (24)	203	80 (39)	-15
By day 1*	252	45 (18)	222	65 (29)	-11

At baseline= on the day of infusion or before receiving study drug.
During infusion=at any time period within the 96 hour infusion period.
By day 1=at baseline and within the first 24 hours.
*****Patients who died by day 1 are excluded from this analysis

Reviewer comment: Patients on heparin appeared to have less treatment benefit than those patients not receiving heparin.

The combined estimate of odds ratio (i.e., by combining "On Heparin" and "Not on Heparin" strata) for "At baseline" subgroup is 0.74 (95% CI: 0.60, 0.91; P=0.005). Furthermore, there is no significant evidence of interaction between mortality and heparin use in this subgroup (P=0.298).

For the "During infusion" subgroup, the combined estimate of odds ratio is 0.73 (95% CI: 0.59, 0.91; P=0.005). In this subgroup, there is some indication of interaction between heparin use and mortality (P=0.026).

Finally, for the last subgroup (i.e., "By Day 1"), the combined estimate of odds ration is 0.74 (95% CI: 0.59, 0.93; P=0.011). Here, the P-value for the interaction between heparin use and mortality is 0.062.

Reviewer comment:

Patients not on heparin had a greater treatment benefit than if on heparin. The use of therapeutic heparin was an exclusion criteria. Low dose heparin use was permitted in the trial, and about 2/3 of the patients received heparin. In the above analysis, we explored whether the use of heparin impacted the size of mortality benefit attributable to rhAPC. rhAPC mortality results in patients on low dose heparin were compared with those in patients not on low dose heparin. Low dose heparin use was categorized in 3 different manners: use at baseline, use any time during rhAPC infusion and by Day 1. The second group includes patients who had heparin begun during study drug infusion, is the group of greatest interest, inclusion of such patients may introduce biases if the use of study drug influenced the decision to start heparin. Therefore both analyses are shown.
The mortality effect of rhAPC was 3-4% in patients on low dose heparin, by either approach. In contrast, the mortality effect of rhAPC was considerably higher in patients not on low dose heparin. So, mortality in patients who received rhAPC was lower than placebo, regardless of whether low dose heparin was used or not, but the treatment benefit was several fold greater in patients that were not on low dose heparin. The study was not designed to assess whether low dose heparin should be used with rhAPC.
However, if the differences between rhAPC effects in patients on low dose heparin (3-4%) and patients not on low dose heparin (9-15%) are real, then the question of whether to administer low dose heparin when using rhAPC could be very important. Potential mechanisms by which low dose heparin might influence the rhAPC effect include: low dose heparin may provide some benefits, leaving less residual benefit for the addition of and low dose heparin use might abrogate some of the benefits from rhAPC, perhaps through synergistic toxicity. A principle way to address this issue is to conduct trials in which patients on rhAPC are properly randomized to receive low dose heparin or not receive low dose heparin.

Therapeutic Heparin

The role of therapeutic doses of heparin (i.e., high dose, intravenous) in sepsis-related DIC is controversial. There have been no adequate controlled trials of therapeutic heparin in this setting. In the phase 3 trial, therapeutic heparin use was an exclusion criterion. Therapeutic heparin and rhAPC should not be administered simultaneously because of bleeding risks.

Treatment Effect by Serum Drug Concentration Quartile Levels

We assessed mortality as a function of APACHE II quartile and steady state concentrations of the drug levels (grouped by quartile). Although numbers in each group are small, mortality appears higher among patients who had the higher concentrations of serum rhAPC. This could reflect the fact that patients who are sickest do not clear drug as quickly.

Table 37. Mortality by APACHE II quartiles and rhAPC steady state concentrations

APACHE II Quartile	Steady State Concentration (n=326) Quartile			
	1(n=81) 0-35 ng/ml Mortality N (%)	2 (n=83) 35-45 ng/ml Mortality N (%)	3 (n=81) 45-62 ng/ml Mortality N (%)	4 (n=81) 62-390 ng/ml Mortality N (%)
1	2/27 (7)	1/15 (7)	1/15 (7)	5/12 (42)
2	4/22 (18)	1/18 (6)	5/20 (25)	6/23 (26)
3	5/20 (25)	3/26 (12)	4/22 (18)	5/25 (20)
4	1/12 (8)	9/24 (38)	6/24 (25)	11/23 (52)
Mean APACHE II	22	27	26	26
Median APACHE II	22	26	26	25

To avoid many groups with small numbers of patients in each, we combined the first and second quartiles and third and fourth quartiles of drug steady state concentrations. The table below provides the data on mortality and APACHE II quartile according to whether patients fell above or below the median of the steady state concentration (45 ng/ml).

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Table 38. Mortality by APACHE II quartiles and rhAPC steady state median concentrations

APACHE II Quartile	Steady State Concentration (n=326)	
	Below Median Mortality (%)	Above Median Mortality (%)
1	3/42 (7)	6/27 (22)
2	5/40 (13)	11/43 (26)
3	8/46 (17)	9/47 (19)
4	10/36 (28)	17/45 (38)

Safety data on steady state levels and AEs will be presented later under the safety section rhAPC Steady–State.

Reviewer comment: Regardless of the APACHE II quartile, mortality appears to be higher in patients who are at the higher steady state drug concentration quartiles. We combined the quartiles, divided them by the median value and noted the mortality was still higher in the higher steady state drug concentrations, again possibly reflecting the lower plasma clearance in the sickest patients.

Treatment Effect and Biomarkers

Presented below are data on treatment effect and five baseline levels of biomarkers (Il-6, ATIII activity, ATIII level, Factor V Leiden, Factor V Hong Kong). There appeared to be a rhAPC treatment benefit across all subgroups.

Table 39. 28-day all-cause mortality subgroup analyses for selected biomarkers

	rhAPC (850)		Placebo (840)		Relative Risk (RR)	95% CI for RR
	Total N	N (%)	Total N	N (%)		
Il-6 Baseline Quartile						
1st (<143.9 pg/ml)	191	20 (10)	217	48 (22)	0.47	0.29, 0.77
2nd (143.91-491.56 pg/ml)	220	58 (26)	189	50 (26)	1.00	0.72, 1.38
3rd (492-2570 pg/ml)	207	59 (29)	202	67 (33)	0.86	0.64, 1.15
4th (>2574 pg/ml)	209	65 (31)	200	87 (44)	0.72	0.55, 0.92
Antithrombin Baseline Deficiency						
Deficient	655	166 (25)	618	201 (33)	0.78	0.66, 0.93
Not deficient	139	28 (20)	146	39 (27)	0.75	0.49, 1.16
Antithrombin Baseline Activity Quartile						
1st (<0.44)	212	68 (32)	186	83 (45)	0.72	0.56, 0.93
2nd (0.45-0.59)	202	48 (24)	191	62 (32)	0.73	0.53, 1.01
3rd (60-0.74)	182	41 (23)	188	40 (21)	1.06	0.72, 1.56
4th (=0.75)	198	37 (19)	199	55 (28)	0.68	0.47, 0.98
Factor V Leiden Mutation for APC resistance						
Negative	768	190 (25)	768	238 (31)	0.80	0.68, 0.94
Positive	33	4 (12)	32	5 (16)	0.78	0.23, 2.63
Factor V Hong Kong Mutation for APC resistance						
Negative	794	193 (24)	785	234 (30)	0.82	0.69, 0.96
Positive	1	1 (100)	2	1 (50)	2.00	0.50, 8.00

These data, along with additional biomarkers, are displayed in the figure below.

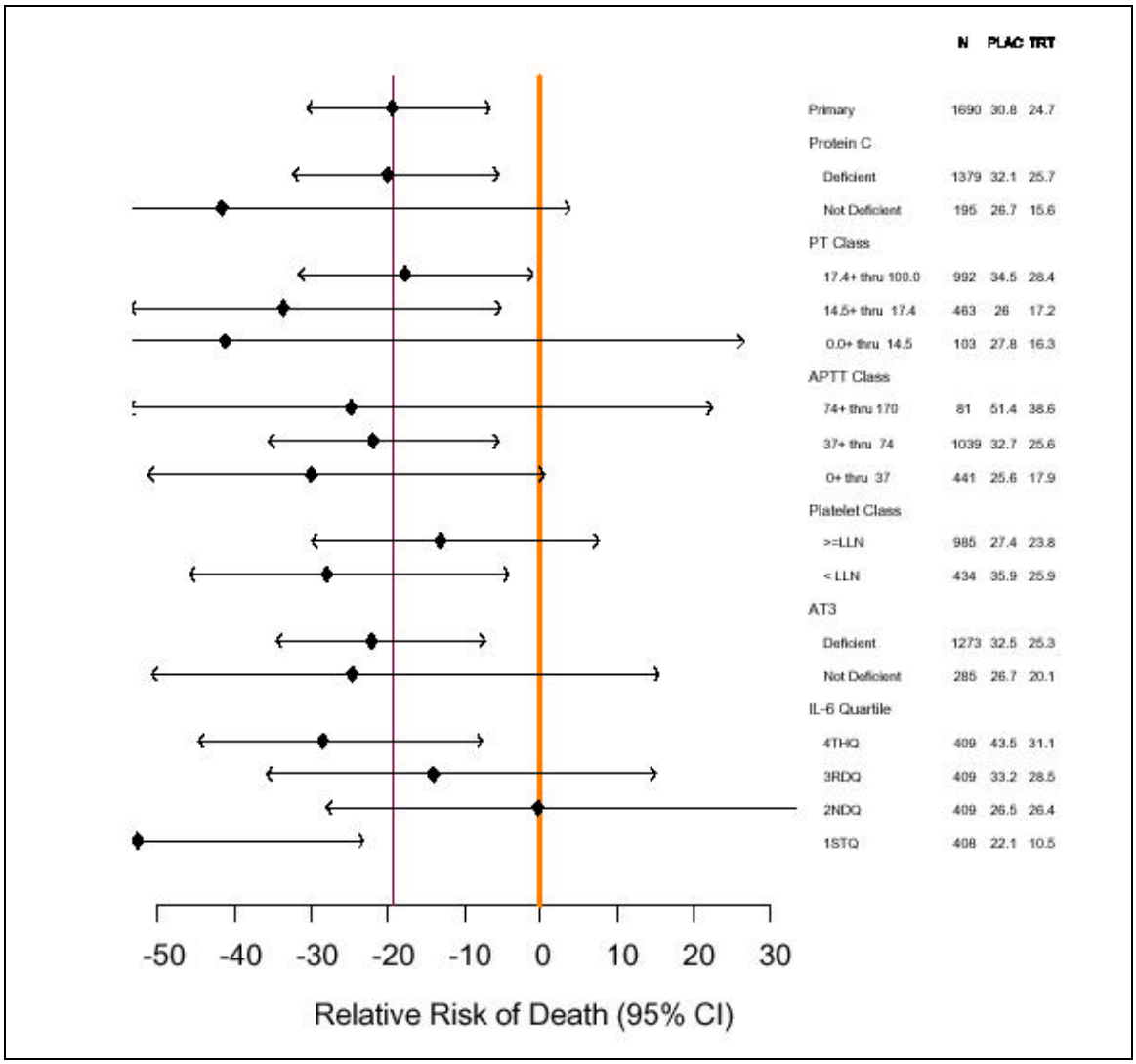

Figure 9. 28-day all-cause mortality across subgroups defined by biochemical measures of baseline disease severity

D-dimer Analyses

D-dimer levels are a marker of thrombin generation. Lilly used D-dimer levels as a marker of drug effect, and the suppression of levels was the rationale for dose selection. During the period of infusion, D-dimers were suppressed in patients on rhAPC as compared to placebo patients. Levels approached, but did not fully return to baseline at the end of the infusion. Data are not available to validate D-dimer levels as a surrogate for mortality.

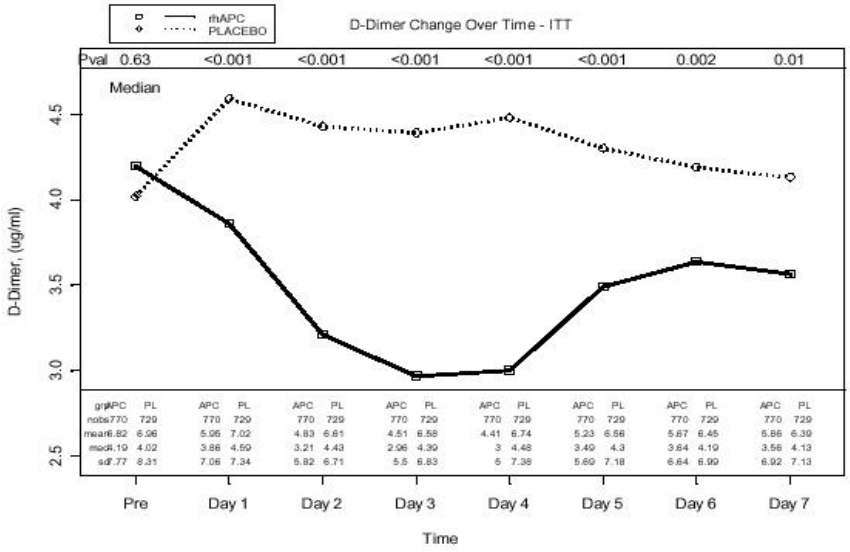

Figure 10. Median D-dimer levels on study days 1 through 7

Treatment Effect and Disease

Table 40. 28-day all-cause mortality in subgroups according to selected baseline measures of disease severity

	rhAPC (850)		Placebo (840)		Relative	95% CI
	Total N	N (%)	Total N	N (%)	Risk (RR)	for RR
ARDS						
No	725	173 (24)	706	216 (31)	0.78	0.66, 0.93
Yes	125	37 (30)	134	43 (32)	0.92	0.64, 1.33
Ventilator						
No	227	40 (18)	188	43 (23)	0.77	0.52, 1.13
Yes	623	170 (27)	652	216 (33)	0.82	0.70, 0.97
Immunocompromised						
No	763	184 (24)	771	235 (30)	0.79	0.67, 0.93
Yes	87	26 (30)	69	24 (35)	0.86	0.54, 1.36

There appears to be a rhAPC treatment benefit in all groups.

Treatment Effect and Microbiology/Site of Infection

The table below is a summary of the site of infection, Gram stain and type of culture obtained at baseline for the treatment groups. Neither a differential treatment effect nor any trends were noted. There appeared to be a beneficial effect of rhAPC treatment in most subgroups. In most subgroups with a relative risk > 1, the numbers of patients are too small to draw meaningful conclusions. The exceptions are patients who present with urinary tract infections (RR=1.01), suggesting little or no benefit (note that this observation has also been made in trials of other agents for sepsis) and in patients where the gram stain could not be confirmed as to whether it was an aerobic or anaerobic infection.

Table 41. 28-day all-cause mortality subgroup analyses for baseline microbiology data

Variable	rhAPC (850)		Placebo (840)		Relative Risk	95% RR for CI
	Mortality		Mortality			
	Total N	N (%)	Total N	N (%)		
Presumed Site of Infection						
Blood	45	11 (24)	42	20 (48)	0.51	0.28, 0.94
Bone/Joint	3	0 (0)	8	4 (50)	0.25	0.02, 3.62
CNS	20	1 (5)	19	3 (16)	0.32	0.04, 2.79
Gynecologic	4	1 (25)	4	0 (0)	3.00	0.16, 57.37
Head/EENT	4	1 (25)	4	0 (0)	3.00	0.16, 57.37
Intra-Abdominal	170	47 (28)	167	51 (31)	0.91	0.65, 1.26
Lung	456	114 (25)	450	151 (34)	0.75	0.61, 0.91
Other	20	4 (20)	15	1 (7)	3.00	0.37, 24.17
Pleural	5	1 (20)	8	1 (13)	1.60	0.13, 20.22
Skin/skin structure	23	8 (35)	28	8 (29)	1.22	0.54, 2.74
Urinary Tract	85	18 (21)	86	18 (21)	1.01	0.57, 1.81
Vascular Catheter	9	4 (44)	6	2 (33)	1.33	0.35, 5.13
Positive Blood Culture						
No	572	133 (23)	567	166 (29)	0.79	0.65, 0.97
Yes	278	77 (28)	273	93 (34)	0.81	0.63, 1.05
Positive Bacterial Culture						
No	285	73 (26)	271	88 (33)	0.79	0.61, 1.03
Unknown	3	3 (100)	2	1 (50)	2.00	0.50, 8.00
Yes	562	134 (24)	567	170 (30)	0.80	0.66, 0.97
Positive Gram Stain Bacterial Culture						
Mixed Gram	133	29 (22)	117	31 (27)	0.82	0.53, 1.28
No Bacterial Expo	285	73 (26)	271	88 (33)	0.79	0.61, 1.03
Pure Gram negative	185	45 (24)	196	56 (29)	0.85	0.61, 1.19
Pure Gram Positive	219	50 (23)	211	69 (33)	0.70	0.51, 0.95
Unconfirmed Gram	28	13 (46)	45	15 (33)	1.39	0.78, 2.47
Positive Anaerobic Bacterial Pathogen Culture						
Mixed Aer/aner	37	5 (14)	32	6 (19)	0.72	0.24, 2.14
No Bacterial Expo	285	73 (26)	271	88 (33)	0.79	0.61, 1.03
Pure Aerobic	482	116 (24)	485	147 (30)	0.79	0.64, 0.98

Pure Anaerobic	16	3 (19)	6	2 (33)	0.56	0.12, 2.58
Unconfirmed Aer/aner	30	13 (43)	46	16 (35)	1.25	0.71, 2.20
Positive Viral Culture						
No	838	204 (24)	827	254 (31)	0.79	0.68, 0.93
Unknown	9	5 (56)	11	4 (36)	1.53	0.58, 4.05
Yes	3	1 (33)	2	1 (50)	0.67	0.08, 5.54
Positive Fungal Culture						
No	772	181 (23)	767	231 (30)	0.78	0.66, 0.92
Unknown	6	3 (50)	9	3 (33)	1.50	0.44, 5.09
Yes	72	26 (36)	64	25 (39)	0.92	0.60, 1.43
Positive Parasite Identification						
No	840	205 (24)	829	255 (31)	0.79	0.68,0.93
Unknown	9	5 (56)	11	4 (36)	1.53	0.58, 4.05

Aer=anerobic. Aner=anerobic. EENT=eye, ear, nose and throat.

Treatment Effect and Steroid Exposure

Patients who are seriously ill with sepsis may receive steroids. The protocol did not specifically exclude steroid use. It is conceivable that steroid use may confound the results. The table is an analysis of mortality according to whether the patient received concomitant steroids. In the analysis, concomitant steroid exposure was defined as the administration of steroids at any time during the study drug infusion period.

Drugs included in the steroid definition: cortisone, dexamethasone, dexamethasone phophate, dexamethasone sodium phosphate, fludrocortisone, fludrocortisone acetate, hydrocortisone, hydrocortisone acetate, hydrocortisone hydrogen succinate, methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, methlyprednisolone, methlyprednisolone acetate, methlypredisolone sodium succinate, prednisolone, prednisolone acetate, prednisone.

Table 42. Mortality by baseline steroid exposure

	rhAPC N (%)	Placebo N (%)
Steroids	238 (28)	227 (38)
No steroids	612 (24)	613 (28)

Interaction p-value=0.304

Table 43. Mortality by steroid exposure during study drug infusion period

	rhAPC N (%)	Placebo N (%)
Steroids	276 (30)	282 (38)
No steroids	574 (22)	558 (27)

Interaction p-value=0.748

Reviewer comment: Mortality was lower on rhAPC than placebo whether or not patients received steroids at baseline or during the infusion period.

Treatment Effect in US Sites

An analysis was conducted of patients enrolled at US sites (n=705) only. A mortality rate was shown of (86/352) 24% on rhAPC compared to (116/353) 33% on placebo. The mortality in non-US sites (n=985) was (124/498) 25% on rhAPC and (143/487) 29% on placebo.

Functional Status Data–Survivors

Subject location at baseline (prior to hospitalization for sepsis) is presented below. In both treatment groups, approximately 80% of the patients were at home and approximately 10% were already in a hospital prior to study entry. More subjects who received rhAPC survived and their overall functional capacity was similar to survivors in the placebo group. Despite the increased survival rate in the rhAPC arm, sepsis is a devastating event with only 25% of the total enrolled subjects achieving discharge home to an un-assisted life style at day 28 (compared to the 80% who were at home) prior to the sepsis event.

Table 44. Subject location at baseline prior to hospitalization

	rhAPC (850)		Placebo (840)		Total (1690)	
	N	(%)	N	(%)	N	(%)
Acute Care Hospital	79	(9)	78	(9)	157	(9)
Home	689	(81)	663	(79)	1352	(80)
Other	34	(4)	28	(3)	62	(4)
Skill Nursing Home	48	(6)	71	(9)	119	(7)

Table 45. Subject location after discharge-survivors

	rhAPC (640)		Placebo (581)		Total (1221)	
	N	(%)	N	(%)	N	(%)
Home – No Supp.	123	(19)	107	(18)	230	(19)
Home – Paid Supp.	44	(7)	39	(7)	83	(7)
Home - Unpaid Supp.	95	(15)	96	(17)	191	(16)
Not Discharged	270	(42)	234	(40)	504	(41)
Other Hospital	32	(5)	29	(5)	61	(5)
Skill Nursing Home	76	(12)	76	(13)	152	(12)

Table 46. Subject location at study day 28-survivors

	rhAPC (640)		Placebo (581)		Total (1221)	
	N	(%)	N	(%)	N	(%)
Home – No Supp.	158	(25)	144	(25)	302	(25)
Home – Paid Supp.	38	(6)	35	(6)	73	(6)
Home - Unpaid Supp.	79	(12)	78	(13)	157	(13)
Other Hospital	23	(4)	20	(3)	43	(4)
Skill Nursing Home	61	(10)	66	(11)	127	(10)
Study Hospital	281	(44)	238	(41)	519	(43)

Reviewer comment: No further long-term follow up data were available beyond 28 days. Lilly has committed to obtain longer follow up for the patients enrolled in PROWESS.

The number of days that patients were free from ventilator use, vasopressors, SIRS, ICU and hospital care are listed below. The survivors of sepsis who received rhAPC treatment

were comparable to the survivors in the placebo group. The rhAPC treated subjects were not on ventilators longer nor did they require vasopressors longer.

Table 47. Vasopressor, ventilator, SIRS, ICU and hospital free days survivors only

	rhAPC (640)	Placebo (581)
Mean		
Vasopressor	25	25
Ventilator	18	18
SIRS	12	12
ICU	16	16
Hospital	8	8
Median		
Vasopressor	27	27
Ventilator	22	22
SIRS	11	12
ICU	19	20
Hospital	7	6

Patients treated with rhAPC who survived the sepsis episode did not appear to function at a decreased level or require more support than those treated with placebo.

Table 48. Patient vasopressor, ventilator, ICU and hospitalization status (%)

		rhAPC (640) %	Placebo (581) %
Vasopressor	Baseline	59	62
	Day 28	2	2
Ventilator	Baseline	71	75
	Day 28	14	15
ICU	Baseline	100	100
	Day 28	16	14
Hospital	Baseline	100	100
	Day 28	43	41

Reviewer comment: No information was available on the hospital type, that is whether large, small, academic, or community at baseline. Therefore we were unable to determine whether there was any difference in outcome based on the type of hospital where the patient was admitted and treated.